BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 9 1960

RECENT ADVANCES IN VIRUS INFECTIONS: THE NEW ERA IN VIROLOGY*†

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This paper describes some of the advances in knowledge of virus infections of man, with particular reference to those new diseases discovered in the last few years, mainly by the use of improved technical methods.

It may be claimed that virus diseases are now the most prevalent of the microbial infections of man, and by failure to respond to antibiotics they stand out in marked contrast to the bacterial infections. The only effective method of control of most of the virus diseases is prophylactic vaccination, and this method has already proved effective against some infections.

The New Viruses

Twenty years ago only 36 antigenically distinct human viruses were known, and 14 of these could not be propagated regularly in the laboratory—that is, the viruses of molluscum contagiosum, warts, herpes zoster, measles, rubella, varicella, infectious hepatitis, serum hepatitis, trachoma, inclusion conjunctivitis, common cold, Australian X disease, dengue, and sandfly fever (Table I). It is small wonder, therefore, that the study of virus infections was mainly an academic pursuit and of little concern to the physician in his daily practice.

During 1940–59 the situation changed significantly, with the discovery of an additional 116 antigenically distinct human pathogenic viruses, all of which can be easily cultivated in the laboratory (Table II). Over 90 of these were discovered in the last 10 years of the period.

As a further advance, many of the viruses already known in 1939 have more recently been adapted to growth in the laboratory—that is, the viruses of herpes zoster, measles, varicella, trachoma, inclusion conjunctivitis, common cold, Australian X (Murray Valley) encephalitis, dengue, and sandfly fever.

At the present day, only five important human viruses have not been propagated in the laboratory—the viruses of molluscum contagiosum, warts, infectious hepatitis, serum hepatitis, and rubella.

Many of the viruses recently discovered are the cause of acute infections commonly encountered in medical practice, and it may be said that viruses have now been established as affecting almost all the organs of the body. It is evident that viruses as a group cause a much wider range of pathological lesions than had been recognized earlier. For example, viruses of the Coxsackie family have been shown to cause acute myocarditis and pericarditis, and some of the insect-transmitted viruses to cause acute gastro-intestinal haemorrhage.

Virus infections are commonly regarded as being acute and self-limiting, with few sequelae. The recent demonstration that acute myocarditis and pericarditis may be caused by viruses, with other evidence of the tissue tropism of viruses, emphasizes the need to investigate the role of these agents in certain forms of subacute and chronic illness—for example, of the heart, vessels, lungs, central nervous system, liver, and gastro-intestinal tract.

Methods for the laboratory diagnosis of virus diseases have been greatly improved and made more generally available. No longer is the study of viruses a purely academic exercise. On the contrary, medical virology is now much concerned with the problems of the practising doctor, particularly in laboratory diagnosis and the development of preventive vaccines.

Advances in Methods of Studying Virus Infections

The Suckling Mouse Technique

A major technical advance, reported in 1948 by Dalldorf and Sickles, was the use of suckling mice. The widespread use of this technique led to the recognition of two major families of Coxsackie virus known as groups A and B. The 19 antigenically distinct types of Coxsackie A virus produce myositis in the limbs and thorax of the baby mouse. The five types of Coxsackie B cause inflammatory changes in the dorsal fat, brain, and pancreas.

Modern Tissue-culture Techniques

The second important development, more accurately described as an improvement of an old technique, was reported in 1949 by Enders, Weller, and Robbins. This team showed that poliovirus would grow in "suspended cell" tissue cultures of minced human embryonic tissue in small conical flasks. The infected tissue fragments slowly degenerated, and in due course stopped metabolizing.

It was soon found that cultures prepared from fragments of tissue planted on the wall of test-tubes were more suitable for the demonstration of the degeneration produced by poliovirus. When such cultures were infected with throat washings or stools of cases of polio

*Based on a paper delivered at the Joint Annual Meeting of the Canadian and British Medical Associations, Edinburgh, 1959.

†The research work of the author has, in recent years, been financed by grants from the National Health Grants Program of the Canadian and Ontario Governments, and from the Connaught Medical Research Laboratories, University of Toronto.

the outgrowth of new cells of the culture degenerated within a few hours. This so-called "cytopathogenic change" could be readily seen under the microscope in wet or stained preparations, and was specifically prevented by the addition of polio antibody.

The essential novelty of the Enders technique was the demonstration that the presence of a virus could be detected by the simple process of examining tissue cultures in test-tubes under a microscope. At one stroke many of the previous technical difficulties of the virologist were removed, and there became available a simple, accurate, inexpensive, and rapid test for the presence of a virus and for specific antibody.

Another major advance was made in 1953, when it was reported that a more sensitive type of culture can be prepared from suspensions of human or monkey kidney extracted with trypsin. Epithelial cells liberated by the enzyme grow in the form of thin sheets of cells in test-tubes. HeLa epithelial cells, originally derived from a carcinoma of the cervix, have also proved sensitive to the presence of poliovirus, as have other cell lines propagated in the laboratory.

Epithelial cells can also be grown in the form of a continuous sheet in Petri dishes. When poliovirus is placed on such sheets, as first shown by Dulbecco, it induces degeneration of the cells with the formation of areas of lysis, or plaques, easily seen with the naked eye. These plaques are analogous to the plaques of bacteriophage growing on cultures of sensitive bacteria. With this new method the virologist has available one of the basic techniques of the bacteriologist, and can obtain "colonies" of viruses, which can be subcultured to yield pure cultures. Sabin has used this technique in his experiments on the selection of polioviruses with greatly reduced virulence for the central nervous system.

At this point it may be mentioned that modern tissue-culture techniques have been rendered practical by the use of antibiotics in the culture media, especially penicillin and streptomycin. No longer is it necessary to take elaborate precautions to prevent contamination of tissue cultures by airborne micro-organisms. The preparation of tissue cultures has become almost as routine as the preparation of blood-agar plates.

TABLE I.—*Human Viruses Discovered by* 1939

Name of Virus Family	Name of Species of Virus
Dermotropic viruses	Molluscum contagiosum*† Warts*† Herpes simplex Herpes zoster*
Exanthem-producing viruses	Measles* Rubella*† Varicella* Variola
Hepatitis-producing viruses	Infectious hepatitis*† Serum hepatitis*†
Basophilic viruses related to psittacosis virus	Lymphogranuloma Psittacosis-ornithosis Trachoma* Inclusion conjunctivitis*
Myxoviruses (haemagglutinating viruses)	Influenza (A classic) Mumps
Other respiratory viruses	Common cold*
Arbor viruses (arthropod-borne viruses)	North American equine encephalitis (Eastern type) ,, ,, ,, ,, (Western ,,) St. Louis encephalitis Japanese B ,, Australian X disease* Louping ill Russian spring-summer encephalitis Yellow fever Dengue ,, (single type)* West Nile Bwamba Rift Valley fever Sandfly fever (single type)*
Other neurotropic viruses	Rabies Poliomyelitis type 1 ,, ,, 2 ,, ,, 3 Virus B Lymphocytic choriomeningitis
Total ..	36

* In 1939 these viruses could not be propagated regularly in experimental animals, embryonated eggs, or tissue cultures.
† These viruses have still not been adapted to regular propagation in the laboratory.

Application of the Newer Tissue Culture Techniques

Though the original work on the growth of viruses in the newer types of tissue culture was done with polio-

TABLE II.—*Human Viruses Discovered in the Period* 1940–59

Name of Virus Family	Name of Species of Virus	No. of Antigenic Types	Major Clinical Features
Basopnilic viruses related to psittacosis virus	Meningopneumonitis	1	Virus pneumonia
	Pneumonia virus of mice	1	
	San Francisco	1	
	Louisiana	1	
	Illinois	1	
Myxoviruses (haemagglutinating viruses)	*Influenza viruses*		
	Influenza (A prime)	1	Influenza
	,, (Asian)	1	
	,, B	1	
	,, C	1	
	Parainfluenza viruses		
	Sendai	1	Upper respiratory illness; croup
	Croup-associated	2	
	Haemadsorption	2	
Other resiratory viruses	Chimpanzee coryza agent	1	Upper respiratory illness
	JH (2060)	1	
	Uppsala	1	
Arbor viruses (group A of Casals)	Chikungunya	1	Dengue-like pains
	Mayaro	1	Fever
	Middelburg	1	—
	Semliki Forest	1	—
	Sindbis	1	—
	Venezuelan equine encephalitis	1	Fever; encephalitis
Arbor viruses (group B of Casals)	Dengue (additional type)	1	Dengue
	Murray Valley	1	Encephalitis
	Ilheus	1	,,
	Bi-undulant fever	1	Fever; meningitis
	Omsk haemorrhagic fever	1	,, haemorrhages
	Central European encephalitis	1	Meningo-encephalitis
	Kyasanur Forest	1	Fever; haemorrhages
	Powassan	1	Encephalitis
	Uganda S	1	—
	Zika	1	Fever
	Ntaya	1	—
	Spondweni	1	—
	Wesselsbron	1	Fever
Arbor viruses (group C of Casals)	Apeu	1	Fever or subclinical only
	Caraparu	1	
	Maguari	1	
	Murutucu	1	
	Oriboca	1	
Arbor viruses (ungrouped)	Sandfly fever (additional type)	1	Sandfly fever
	California encephalitis	1	Encephalitis
	Bunyamwera	1	—
	Colorado tick fever	1	Fever
	Crimean haemorrhagic fever	1	Fever; haemorrhages
Enteroviruses (enteric viruses)	Coxsackie group A	19	Herpangina; fevers
	,, ,, B	5	Myalgia; meningitis
	Echo	25	Meningitis; rashes
Adenoviruses	Adenovirus	18	Myalgia; pharyngitis; coniunctivitis
Miscellaneous viruses	Contagious pustular dermatitis	1	Pustular lesions
	Cytomegalic inclusion disease	1	Generalized infection
	Mengo virus	1	Encephalitis
Total ..		116	

virus, it was soon found that many other viruses would grow and produce characteristic cytopathogenic changes. To some extent the nature of an infecting virus can be identified by examination of the microscopic changes induced in tissue cultures.

For example, poliovirus, Coxsackie, and Echo viruses produce an eosinophilic mass in the cytoplasm, and the nucleus becomes pyknotic, shrunken, and pushed to one corner of the cell. Measles virus causes the epithelial cells to become aggregated into giant cells or syncytia, the individual nuclei containing acidophilic inclusions. Herpes simplex, herpes zoster, and varicella viruses also cause the formation of giant cells, but they are smaller, with fewer nuclei. In the early stage of infection the nuclei contain basophilic inclusions; later, the well-known eosinophilic Lipschütz inclusions appear. Adenoviruses also produce intranuclear inclusions, and a characteristic "rosette"-like rearrangement of the nuclear chromatin. Vaccinia virus produces eosinophilic Guarnieri inclusions in the cytoplasm.

An application of even greater importance than the identification of viruses already well recognized has been the discovery of over 50 antigenically distinct new viruses that grow only in tissue culture. These viruses fall into the families of adenoviruses, Echo viruses, croup-associated viruses, haemadsorption viruses, and several others (Table II).

Another important application of tissue cultures has been the mass production of virus-infected fluids for processing into vaccines. The method introduced by my colleagues at the Connaught Medical Research Laboratories, University of Toronto, early in 1953 is still in use, with modifications, in Canada and many other parts of the world, for the production of polio vaccine. Monkey-kidney tissue is finely minced and suspended in about 750 ml. of a synthetic nutrient such as Mixture No. 199 of Morgan, Morton, and Parker. The material is placed in a large diphtheria-toxin-production bottle and rocked; after a few days the fluid is replaced with fresh nutrient, and virus is then added. High yields of virus are obtained from the fluid a few days later.

Essentially the same simple technique has been used by Hilleman and by Huebner in the production of vaccines against the adenoviruses, and may well serve for the production of vaccines against measles, and some of the viruses which cause colds.

Advances in Study of the Arbor Viruses

Although I have stressed the advantages of tissue cultures in the study of viruses, about 20 new arthropod-borne (arbor) viruses pathogenic for man have been isolated since 1939 by the standard technique of inoculation of mice. The arbor viruses contain antigens that agglutinate red cells *in vitro*, and the nature and distribution of these antigens can be studied by tests in which this agglutination is prevented by antiserum. Casals and Theiler have found that the arbor viruses can be arranged in four antigenically distinct families by means of this haemagglutination inhibition test (Table II).

Laboratory Diagnosis of Virus Infections

The laboratory diagnosis of virus infections is made by two methods. In the direct method the causal virus is isolated from pathological specimens. In the indirect method evidence of infection is afforded by the demonstration that serum antibodies develop in convalescence. The modern trend is to concentrate on the direct method of diagnosis, by isolation of the causal virus from pathological specimens, if possible in tissue cultures. If the virus is one that produces specific cytopathogenic changes, identification is often possible within two to four days.

In the past few years facilities for virus diagnosis have been provided by university, hospital, and public health laboratories on a considerable scale.

In Canada, for example, many of our Provincial Government Public Health Laboratories now provide to practitioners a diagnostic service for virus infections. In several of the teaching departments of universities and in the larger teaching hospitals there are also laboratories where diagnostic tests can be done. The Virus Laboratories of the Federal Department of National Health and Welfare in Ottawa serve as a reference centre for identification of strains and for the preparation of diagnostic antigens and sera.

This development is remarkable when one recalls that ten years ago there were only two or three laboratories in Canada where virus diagnostic tests could be performed.

In the diagnosis of virus infections in the laboratory, main emphasis should be placed on isolation and precise identification of the causal virus as speedily as possible. The physician is offered a presumptive diagnosis based on the isolation of a virus from a patient. The interpretation of the significance of such an isolation must be made by the attending physician.

Subclinical infection with many of the new viruses is common, and isolation of a virus from a patient may merely represent excretion from an earlier infection some weeks before. The isolation of virus from blood, cerebrospinal fluid, organ suspension, or skin lesions is much more significant than isolation from throat or stool.

Virus infections usually occur in epidemics, and the isolation of the same antigenic type of virus from several acutely ill persons affords strong evidence for the aetiological role of that virus.

In the great majority of persons infected with a virus, antibody develops in the blood within 7 to 14 days of onset. This can be tested by the complement fixation, virus neutralization, or haemagglutination-inhibition techniques. The demonstration that antibody increases in level fourfold or more during convalescence is usually acceptable evidence for current infection. Though serological tests are essential in research studies, their value to the practitioner is limited because the tests are retrospective.

Poliomyelitis and Other Enteroviruses

Concept of the Enterovirus Family

Study of the biological properties of the poliomyelitis, Coxsackie, and Echo viruses, as manifested both in laboratory hosts and in human beings, has led to the concept of the "enterovirus family," the members of which proliferate readily in the gastro-intestinal tract of man. The fifty or so distinct antigenic types of poliovirus, Coxsackie virus, and Echo virus are now all classified into one family. Some of the common properties of enteroviruses are as follows: the members are of the same order of size (30 millimicrons), are nucleoproteins, and resist treatment with ether. Most of

the members of the family grow in tissue cultures and produce identical cytopathogenic changes.

Epidemiologically, the enteroviruses mainly cause infections in childhood, and are transmitted by close contact, droplets, and faecal contamination. One strain of enterovirus may cause several clinical types of illness even in individual family groups. In the temperate parts of the world infections are much commoner in the summer and autumn than in the colder months.

In any given year, one enterovirus type seems to predominate in each locality. For example, as shown in Table III, this has been the case in the Toronto area of Southern Ontario during 10 years of continuous study of epidemic enterovirus infections.

TABLE III.—*Enteroviruses Epidemic in Toronto Area, 1949–58*

	Polio	Coxsackie	Echo
1949	Type 1		
1950		B1	
1951	,, 1	B2	
1952		B4	
1953	,, 1		
1954		B2	
1955		B2	
1956			Echo 9
1957			,, 9
1958		B5	

Pathogenesis of Enterovirus Infections

The enteroviruses have a common mechanism of pathogenesis, and studies in the past few years have led to a complete change in thought on the pathogenesis of infection with poliovirus, the most extensively investigated member of the family. Until not so long ago, poliovirus was regarded as a neurotrope, spreading to the central nervous system in nerve fibres, from the point of entry in the pharynx, olfactory mucosa, or gastro-intestinal tract. This concept was developed largely from study of the infected rhesus monkey. In this species the virus does indeed behave as a neurotrope and spreads to the central nervous system by nerve fibres. Rhesus monkeys cannot be infected by feeding virus, and are only susceptible by the intravenous route if very large doses are given.

A major step towards understanding the pathogenesis of polio in man was made when it was demonstrated that cynomolgus monkeys and chimpanzees can be quite readily infected with poliovirus administered in food. The chimpanzee constitutes a particularly close model for the study of the human infection. After the administration of poliovirus in food, these primates develop a gastro-intestinal infection and excrete virus in the throat and faeces. Only about one in ten infected animals becomes paralysed, but the others develop a subclinical infection.

The current concept of the pathogenesis of polio in man has developed from the work of Bodian, Howe, Horstmann, and Sabin on chimpanzees and man. According to this hypothesis, there are four distinct stages in the spread of virus through the body.

In stage 1, after ingestion or inhalation, the virus proliferates in the lymphoid tissue of the pharynx, especially the tonsil, and also proliferates in the intestine, especially Peyer's patches.

In stage 2, virus passes to the regional lymphatic nodes, where further multiplication takes place; some virus then enters the blood-stream to initiate stage 3, the stage of viraemia. During this blood-vascular phase, virus presumably multiplies in the internal organs. The viraemia stage lasts for four to five days, and may be accompanied by fever and a non-specific illness.

Finally, in stage 4, virus enters the target organ—the central nervous system—attacking the ganglionic nerve cells.

Infection may be aborted at any of the stages, and it is probable that only in about one in every hundred infected persons does the central nervous system become attacked. Virus-neutralizing antibody in the blood will prevent the stage of viraemia, and therefore involvement of the central nervous system.

Killed (formalinized) vaccine exerts its protective role through the development of blood antibody, which neutralizes virus that enters the blood. Formalinized vaccine does not prevent stages 1 and 2, and when the vaccinated person is exposed to infection proliferation of virus takes place in the gastro-intestinal tract and lymphatic nodes, with some excretion of virus.

It now appears clear that the immune mechanism in those who have suffered a natural, usually subclinical, infection is different. Such "naturally immune" persons develop a relative state of resistance of the gastro-intestinal tract, so that exposure to virus does not usually lead to any significant degree of gastro-intestinal infection and faecal excretion of virus.

If this concept is correct, the attenuated strains of poliovirus now being widely tested by oral administration may have certain advantages, because they induce two barriers to reinfection—a state of local resistance of the gastro-intestinal tract, and a state of generalized resistance by the circulation of blood antibody.

Studies on the pathogenesis of the other enteroviruses are not nearly so complete, but it is reasonable to infer that the mechanisms are similar. The Coxsackie viruses proliferate in throat and gastro-intestinal tract, and have been isolated from the blood. Coxsackie viruses localize in more "target organs" than does poliovirus—for example, the throat, striated muscles, myocardium, pericardium, brain, and meninges. The target organs in Echo infections appear to be the meninges and skin.

Clinical Features of Enterovirus Infections

The three enteroviruses have a similar mechanism of pathogenesis, and some similarity of clinical features might reasonably be expected. As shown in Table IV, there are nine main groups of clinical feature now attributed to infection with the enteroviruses. It will be noted that paralysis, aseptic meningitis, and summer fevers may be caused by members of all the enterovirus families, and rubelliform rashes by all except poliovirus. It seems likely that further research will lead to a

TABLE IV.—*Spectrum of Clinical Features Caused by Enteroviruses*

Clinical Feature	Causal Agents			
	Polio	Coxsackie A	Coxsackie B	Echo
Paralysis	1, 2, 3	A7, 9	B3, 4, 5	2, 4, 6, 9, 16
Virus meningitis	1, 2, 3	A2, 4, 7, 9	B1 to 5	2, 4, 6, 9, 14, 16
Summer fevers	1, 2, 3	Several types	B1 to 5	Several types
Rubelliform rashes	—	A2, 4, 9, 16	B4	2, 4, 6, 9, 14, 16
Myocarditis	1, 2, 3	—	B2, 3, 4, 5	—
Pericarditis	—	—	B2, 3, 4, 5	—
Herpangina	—	Several types	—	—
Epidemic myalgia	—	—	B1 to 5	—
Diarrhoea	—	—	—	18 and other types

recognition that myocarditis, pericarditis, and other features may sometimes be caused by additional members of the enterovirus family.

The enteroviruses are of considerable importance in these days of widespread immunization against polio. Laboratory investigations show that most of the illnesses reported in vaccinated persons are caused by Coxsackie and Echo viruses. Most of these illnesses are classified clinically as "virus" or "aseptic" meningitis. As shown in Table V, in the Ontario study of illness in vaccinated

TABLE V.—*Ontario Poliomyelitis Vaccine Study*, 1956.* *Reported Cases of Polio and Suspect Polio in Patients Aged 18 and Under*

Type of Illness	Cases of Illness in Groups Designated		
	Vaccinated (840,000)	Unvaccinated (960,000)	Total
1. Paralytic polio	5	71	76
2. Aseptic meningitis (caused by polio virus)	1	9	10
3. Aseptic meningitis (caused by Coxsackie–Echo viruses)	49	54	103
4. Aseptic meningitis (caused by unidentified viruses)	40	37	77

* Brown, W. G., *et al.*, *Canad. med. Ass. J.*, 1958, **79**, 155.

and unvaccinated children, the Coxsackie and Echo viruses played a major part. The considerable protective effect of the vaccine against laboratory-proved polio infection may be noted.

It should be noted that a single strain of enterovirus may cause several different manifestations of illness in a given locality, even in one family. Thus, in 1958 in Toronto, Coxsackie virus B5 was responsible for cases of aseptic meningitis, Bornholm disease, myocarditis, and pericarditis.

The Adenoviruses

The tissue-culture techniques originally introduced for the study of poliomyelitis have been profitably used in the investigation of infections of the respiratory tract and conjunctival sac. In the past six or seven years, workers in Washington, D.C., have firmly established the pathogenic role of another new group of viruses that grow only in tissue culture (Hilleman; Huebner, Bell, and Rowe). These adenoviruses were first recovered from adenoids grown in tissue culture.

The adenoviruses, which occur in nearly 20 different antigenic types, grow particularly well in HeLa cell tissue cultures and cause a characteristic cytopathogenic change, with the formation of intranuclear inclusions. The viruses do not infect experimental animals.

In man, the adenoviruses proliferate in the conjunctival sac, cornea, and upper respiratory tract; occasionally they invade the lung to cause one form of virus pneumonia.

TABLE VI.—*Clinical Entities Caused by Adenoviruses*

Clinical Entity	Main Clinical Features	Type of Adenovirus Usually Involved
Acute respiratory disease of military recruits	Influenza-like illness	3, 4, 7, 14
Virus pneumonia	Pneumonia	1, 3, 4, 7
Pharyngoconjunctival fever of children	Fever, conjunctivitis, pharyngitis	3, 4, 7, 14
Minor respiratory illnesses (colds)	Often with pharyngitis	1 to 5, 7
Epidemic keratoconjunctivitis	Severe infection often with corneal opacities	8
Sporadic follicular conjunctivitis	Sometimes with transient opacities	2, 3, 6 to 10

The adenoviruses cause a wide range of clinical entities, as shown in Table VI, but there are common features, especially pharyngitis, fever, and keratoconjunctivitis.

Adenovirus infections are spread directly or indirectly by infected eye secretions or by droplet infection. There is good evidence that conjunctivitis and keratoconjunctivitis may be spread by contaminated eye solutions, eye instruments, and doctors' and nurses' hands.

Not all of the adenovirus types have yet been established as pathogenic, but several have been so accepted, especially types 3, 4, and 7 in respiratory disease and type 8 in epidemic keratoconjunctivitis.

Laboratory diagnosis is made by isolation of the causal virus from eye secretions, throat washings, or sputum, together with the demonstration of increase in virus-neutralizing or complement-fixing antibodies.

Vaccines have been produced by Hilleman and by Huebner by a method similar to that used in poliomyelitis. These vaccines have proved highly effective in military recruits.

Other New Respiratory Viruses

Continued investigation of cases of respiratory illness by tissue-culture techniques has led to the discovery of several new viruses, such as the croup-associated viruses, haemadsorption viruses, chimpanzee-coryza agent, JH virus, and the Uppsala virus. Two of these groups of virus are of particular interest, croup-associated and the haemadsorption viruses. These viruses are related to influenza virus and cause agglutination of red cells *in vitro*.

The croup-associated viruses were isolated independently in Toronto in 1955 by my colleague Beale, and in Cincinnati by Chanock. In our study, 10 of 15 patients with severe acute laryngotracheobronchitis (croup) yielded cytopathogenic viruses in tissue cultures of human amnion. The viruses produced a syncytial degenerative change. Chanock has shown that there are two major antigenic types of croup-associated virus, and that these are probably causal agents of some cases of croup and of milder upper respiratory illnesses.

The haemadsorption viruses, also isolated by Chanock, grow in tissue culture and produce a syncytial type of cell degeneration. The name "haemadsorption" derives from the fact that when a suspension of red cells is added to infected tissue cultures the cells are adsorbed to the areas where virus is growing.

The haemadsorption viruses appear to cause mild upper respiratory illnesses, bronchitis, as well as croup. It seems probable that many more viruses will be found which have the property of causing mild respiratory illnesses. Already claims have been established for the aetiological role of the chimpanzee-coryza agent, the JH virus, and the Coe virus in common colds and even more severe respiratory illnesses. Andrewes concludes that, though many of these viruses have been thought to produce cold-like symptoms, there is no evidence that they cause a substantial percentage of the "commonest type of common cold."

Recent Advances in the Arthropod-borne Viruses

During the period under review great advances in knowledge have been made in one of the largest group of viruses, the arthropod-borne or arbor viruses. Much

of the new knowledge has come from the Rockefeller Foundation's programme of planned search for these agents in man, mosquitoes, and animal hosts, being conducted vigorously in South America, Trinidad, East Africa, India, and South Africa.

To date, 27 antigenically distinct arbor viruses have been found in nature in South America, 24 in Eastern Africa, 15 in India, Malaya, China, and Indo-China, and 10 in North America. Many of these are of proved infectivity for man and often for wild and domesticated animals. It is certain that many more arbor viruses await discovery.

It has been known for many years that the arthropod-borne viruses can be arranged in various subgroups by standard serological methods, but only within the past few years has a reasonably satisfactory classification been achieved.

Most of the arbor viruses haemagglutinate, and Casals and Theiler have shown that the viruses can be classified into three main groups (A, B, and C) by the haem-agglutination-inhibition reaction; there is also a fourth group of unrelated viruses. Casals and Theiler allocate to group A the following viruses: Eastern, Western, and Venezuelan equine encephalitis viruses and Mayaro virus of Trinidad. Members of group B include the viruses of yellow fever, dengue, St. Louis encephalitis, Japanese B encephalitis, Murray Valley encephalitis, West Nile fever, Ilheus encephalitis, and the members of the Russian spring-summer encephalitis subgroup (louping ill, Omsk haemorrhagic fever, bi-undulant fever, Kyasanur Forest, and the Powassan (Northern Ontario) viruses. The members of group C, isolated in South America, have not yet been established as important causes of disease in man.

Practically all of the arbor viruses produce encephalitis in mice, and are usually isolated by inoculation of these animals rather than tissue cultures. Though the tendency has been to regard many of the arbor viruses as being neurotropic for man, this property is in fact uncommon. Though certain of the arbor virus group cause encephalitis in man, subclinical and abortive non-specific febrile infections are much commoner.

Arbor viruses closely related antigenically may produce a wide range of clinical features. The Russian spring–summer complex of viruses in group B illustrates this point very well. The Russian spring–summer virus causes severe involvement of the nervous system in man, and louping-ill virus behaves likewise in sheep. Infection by the closely related virus of Omsk haemorrhagic fever causes in contrast a febrile illness with marked tendency to gastro-intestinal haemorrhage. Infection with Kyasanur Forest virus of India causes a similar illness to that caused by the Omsk virus, with prostration, myalgia, and gastro-intestinal haemorrhage, but the fatality rate is higher. In bi-undulant fever there are two paroxysms of fever, with an afebrile period of several days intervening; the illness is not fatal.

Conclusions

The past few years have witnessed a remarkable change in virology. Twenty years ago only two dozen viruses could be readily cultivated in the laboratory. Virology was largely an academic subject little concerned with applications to the daily practice of medicine. To-day, the list of viruses infecting man, and that can be readily studied in the laboratory, is about 150, and the number is increasing rapidly. The introduction of new technical methods has led to the discovery of the new viruses, and the same methods are widely used for laboratory diagnosis, which is now almost as practical as bacteriological diagnosis.

Foremost in recent advances has been the introduction of new tissue-culture techniques which have enormously simplified the work of the virologist and extended his scope.

There can be little doubt that in most communities viruses are responsible for more illness than are bacteria. Research of the last few years has proved that many of the common ailments of man are virus infections. Further progress is confidently anticipated.

Summary

This paper reviews some of the advances in knowledge of virus infections, with particular reference to those new diseases discovered in the last few years, mainly by the widespread adoption of the techniques of inoculation of suckling mice and tissue cultures.

In 1939, only 36 antigenically distinct viruses causing human disease were known, and 14 of these could not be propagated at will in the laboratory.

During the period 1940–59, an additional 116 antigenically distinct strains were discovered, over 90 in the latter 10 years of the period.

Only five important known viruses infecting man have not been propagated in the laboratory—the viruses of molluscum contagiosum, warts, infectious hepatitis, serum hepatitis, and rubella.

The contribution of the newer tissue-culture techniques to the study of viruses is emphasized.

Recent advances in knowledge of poliovirus and the other enteroviruses are outlined. Attention is drawn to the similarity of the clinical features caused by the enteroviruses, including paralysis.

The paper includes a review of the prevalence of enterovirus infections in Ontario in the last 10 years.

Finally, recent advances in the knowledge of the arbor viruses, adenoviruses, and other respiratory viruses are described.

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A bequest made by a West Australian doctor for the foundation of a medical research fellowship will become effective this year, 31 years after his death. The bequest was made by a former Chancellor of the West Australian University, Dr. Athelstan Saw, of Perth, whose son had died of diabetes. Dr. Saw, who died in 1929, directed in his will that the research should be conducted in association with a medical school when one was established (as it recently was) at the University in Perth.

VIRUSES, BACTERIA, AND RESPIRATORY DISEASE IN CHILDREN

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The purpose of this investigation was to examine and correlate clinical, bacteriological, and virological information in acute respiratory infection in children.

Few comprehensive studies of this kind have been carried out. Morrison *et al.* (1957), in London, investigated children for both bacterial and virus agents; Graham (1958), in Melbourne, carried out an extensive laboratory investigation of laryngo-tracheo-bronchitis in children. These two groups of workers were unable to study their patients fully and examine them for the new types of parainfluenza viruses which have been isolated over the past six years and more fully classified in the last two years (Kuroya *et al.*, 1953; Chanock, 1956; Beale *et al.*, 1956, 1958; Gardner, 1957; Chanock *et al.*, 1958; Petersen and von Magnus, 1958; Vargosko *et al.*, 1959).

Numerous bacteria have been isolated from the respiratory tract in acute respiratory disease, but the exact role of these organisms is difficult to define, as many of them are found in the throats of apparently normal children.

The Investigation

The investigation included all children suffering from acute respiratory infection admitted to three hospitals in Newcastle—the Royal Victoria Infirmary, the Babies' Hospital, and the Newcastle General Hospital—they numbered 195. The period of investigation extended over six months from January 1, 1959, to June 30, 1959.

The clinical examination and records of the cases were supervised and co-ordinated by one person. The virological examinations were all performed at the Public Health Laboratory, Newcastle; the bacteriological examinations were shared between the Bacteriology Department of the Royal Victoria Infirmary and the Public Health Laboratory.

Methods

Clinical Assessment.—On admission the history was taken, usually from the mother, and the physical signs and the results of early investigations (*x*-ray examination, white-cell counts) were recorded on a special form. Treatment, day-to-day progress, condition on discharge, and final diagnosis were also recorded, and in each case a follow-up appointment was made for between 14 and 21 days after the onset of symptoms, if the child's

discharge had occurred before this. A record of the child's condition at this time was also made.

Bacteriology.—A " cough swab " and a pernasal swab were taken on admission. Because they were plated with the minimum of delay, cough swabs without serum were used. The isolation of *Haemophilus pertussis* was attempted on freshly prepared *Bordet–Gengou* medium from the pernasal swabs. All organisms appearing on blood-agar culture were recorded, especially coagulase-positive *Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae,* and *Streptococcus pyogenes.* A further cough swab was collected at the follow-up examination.

Virology.—A cough swab, taken on admission, was broken into a bijou bottle of Hanks's basic salt solution containing antibiotics, and was frozen at the bedside. For this purpose, each hospital had two vacuum flasks, and these the laboratory refilled with " cardice " daily. Two specimens of blood were taken from every patient —one on admission and one at follow-up.

Serological Techniques.—An overnight complement-fixation technique based on the original method of Fulton and Dumbell (1949), which permitted greater sensitivity and the use of small quantities of sera, was employed, because antibodies in the young are often poorly developed. All sera were screened by the complement-fixation test against the antigens of viruses influenza A, B, and C, psittacosis, the adenovirus group, Sendai, and mumps (virus particle antigen). They were also tested by the same technique against *Rickettsia burneti* and by a modified agglutination test against *Streptococcus* M.G. for atypical pneumonia. Finally, an antigen for parainfluenza type II (croup-associated) was kindly supplied by Dr. Margaret Pereira, of Colindale, and was used if any serum remained.

Culture Techniques.—All specimens were inoculated on the same day into six 11-day-old fertile hens' eggs for the attempted isolation of influenza A, B, and C viruses. At the same time tissue-culture tubes of HeLa cells and monkey-kidney cells were inoculated. HeLa-cell cultures were maintained for 28 days, principally for the isolation of adenovirus; a technique similar to that employed by Munro-Ashman *et al.* (1958) was used for their isolation and identification. A haemadsorption technique based on the original method of Vogel and Shelokov (1957) was employed for the detection of the parainfluenza viruses. Typing sera for these three groups of parainfluenza viruses were supplied by Dr. Margaret Pereira, who also confirmed any positive results. The identification method used was a haemadsorption inhibition test similar to that described by Chanock *et al.* (1958).

Clinical Classification

In this study 195 children were initially examined, but 35 were later excluded because they could not be followed up satisfactorily, and a further 14 because they did not fall into the categories of acute respiratory infection defined below. Three of these 14 children were admitted in typical asthmatic attacks, four had measles, and the remainder proved subsequently to be suffering from some non-respiratory disease. The total number of completed cases available for study was 146. They were divided into five clinical groups.

1. *Upper Respiratory Infections* (coryza, pharyngitis, tonsillitis, otitis media) (28 cases).—These children had signs which were mainly restricted to the upper respiratory tract, though a number had hoarseness or loss of voice but no stridor.

2. *Croup* (6 cases).—Stridor was always present in this group. In addition there was sometimes an associated pharyngitis or tracheobronchitis.

3. *Acute Bronchitis* (37 cases).—This was an illness of moderate severity; there were always rhonchi in the chest, and the children usually had a well-marked wheeze.

4. *Acute Bronchiolitis* (27 cases).—These babies, all of 6 months or under, presented a characteristic clinical picture. They were usually pale, with a distressing continuous cough, respirations were shallow and rapid, the chest was emphysematous, and crepitations were present in all areas of the lung fields. *X*-ray examination of the chest in most cases showed generalized emphysema with occasional linear areas of collapse.

5. *Bronchopneumonia or Segmental Pneumonia* (48 cases).—These children were ill, with rapid breathing, and there was always evidence, clinically or radiologically, of a focus or scattered foci of collapse and consolidation.

Results

The criteria on which evidence of infection with a virus was based were either the isolation of an agent from the throat swab or a fourfold or greater rising titre of complement-fixing antibodies between the initial and convalescent specimen of serum. In many instances both these criteria were satisfied, though three children, admitted to hospital between the seventh and tenth days from the beginning of their illnesses, had high but non-rising titres; these, too, were accepted as diagnostic. Thirty-five cases were accordingly diagnosed as virus infections: 16 were both culturally and serologically positive, and 11 were serologically positive only. In the remaining eight cases a virus was isolated, but in five of them serological examination was incomplete, one patient died in the acute stage of the illness, and in two patients, both under 1 year of age, no antibodies were found.

The bacteria which were regarded as potential pathogens were coagulase-positive *Staph. aureus, H. influenzae, Str. pneumoniae, Str. pyogenes,* and haemolytic streptococci other than group A.

Tables I and II show the clinical classification according to age and severity.

TABLE I.—*Distribution of Clinical Groups According to Age*

Age	Upper Respiratory Infections	Croup	Bronchitis	Bronchiolitis	Pneumonia	Total
0 to 6 months ..	6	0	18	27	19	70
7 to 23 months ..	12	2	13	0	11	38
2 to 5 years ..	4	2	5	0	8	19
Over 5 ,, ..	6	2	1	0	10	19
Total ..	28	6	37	27	48	146

TABLE II.—*Severity of Illness in Relation to Age*

Age	Mild	Moderate	Severe	Deaths	Total
0 to 6 months ..	17	39	9	5	70
7 to 23 months ..	15	22	1	0	38
2 to 5 years ..	2	14	2	1	19
Over 5 ,, ..	3	15	1	0	19
Total ..	37	90	13	6	146

Table III shows the isolation of pathogenic bacteria from the respiratory diseases; owing to multiple isolations from single cases the total isolations exceed the number of cases associated with bacterial pathogens.

TABLE III.—*Incidence of Potential Bacterial Pathogens Within the Clinical Groups*

	Coagulase-positive Staphylococci	*H. influenzae*	*Str. pneumoniae*	Streptococcus	
				Group A	Other Groups
Upper respiratory infection (28) ..	2	8	3	1	5
Croup (6) ..	2	2	0	0	1
Bronchitis (37) ..	10	7	3	1	2
Bronchiolitis (27) ..	8	6	5	0	0
Pneumonia (48) ..	12	11	10	1	2

TABLE IV.—*Incidence of Virus Infection Within the Clinical Groups*

	Influenza			Croup-associated Virus	Adeno-virus	Sendai	Total
	A	B	C				
Upper respiratory infections (28)	1	6	0	1	2	1	11
Croup (6) ..	0	4	0	2	0	0	6
Bronchitis (37) ..	1	2	2	0	0	0	5
Bronchiolitis (27)	0	0	0	0	0	0	0
Pneumonia (48) ..	1	5	1	2	4	1	14*

* An adenovirus and influenza B were isolated from one case.

TABLE V.—*Correlation of Virus and Bacterial Isolations with Age*

Age	No. of Cases	No. with Evidence of Virus	No. with a Bacterial Pathogen
0 to 6 months	70	4 (6%)	36 (51%)
7 to 23 months ..	38	12 (32%)	23 (61%)
2 to 5 years	19	6 (32%)	11 (58%)
Over 5 ,, ...	19	13 (68%)	11 (58%)

Table IV indicates the distribution of virus infections in the clinical groups. One case of segmental pneumonia, from which influenza B virus was isolated, also had an adenovirus. The serum available was only sufficient to titrate against influenza B, and this showed a diagnostic rise in titre.

Table V shows the percentage of infections, bacterial and virus, according to age.

Children with Croup-associated Virus

The appearance of the croup-associated virus of Chanock and Beale in this series merits a brief clinical description of the cases in which it was found.

The virus was isolated from four children, in two of whom there were positive serological findings. In one child, though no virus was cultured, the sera were positive in both the child and his mother.

Child of 7 months with pharyngitis. There was a feverish illness with coryza of two days' duration, and physical signs were restricted to the upper respiratory tract. No family history of infection was present. Croup-associated virus was isolated and the specific antibodies showed a rise.

Child of 18 months with croup. The illness began with a febrile convulsion. Coryza and stridor developed on the second day, the whole illness lasting three days. One sibling had a slight coryza at the same time. Croup-associated virus was isolated, but insufficient serum remained to test.

Child of 5 years with croup. Fever, cough, and moderate stridor developed, lasting nearly a week. Previous attacks of a similar nature had occurred, but there was no family history of infection. Croup-associated virus was isolated and the serological findings were positive.

Child of 9 months with bronchopneumonia. This child had a cough with vomiting and fever three days before admission and became breathless. The illness was of moderate severity with crepitations in the left upper and right lower lobes; *x*-ray examination of the chest showed diffuse mottling in the right lower lobe. The illness lasted about eight days; there was no family history of infection. Croup-associated virus was isolated, but the serological findings were negative.

Child aged 2½ years with bronchopneumonia. The illness began as a cold one week before admission. Cough, fever, and increasing breathlessness developed. At the time of the child's admission the mother also had an acute coryza. The child was moderately ill with crepitations and diminished air entry in the right lower lobe. *X*-ray examination of the chest showed patchy consolidation of both right upper and lower lobes with slight pleural effusion. The illness persisted for two weeks and radiological signs had not completely cleared at follow-up examination. No virus was isolated from cough swabs, but both child and mother showed a rise in the antibody content of the serum.

Discussion

In this investigation we were trying to determine the relation between differing patterns of clinical illness and the virus and bacterial agents associated with them.

Examination of the results revealed two features. The first showed that, except in acute bronchiolitis, there was an assortment of viruses identified in each clinical group, but no particular virus predominated. Moreover, no single virus was associated with any particular clinical finding such as meningism, muscle-aching, type of fever, or abnormal white-cell count. The second feature was the difference in the virological findings in the different clinical groups. This was most striking in acute bronchiolitis, for in the 27 cases of this disease no virus agent was identified either culturally or serologically. This contrasts sharply with croup, in which a virus was found in all six cases—influenza B virus in four and croup-associated virus in two.

Evidence of a virus was found in 11 out of 28 cases of upper respiratory infections, in 14 out of 48 cases of pneumonia, and in 5 out of 37 cases of acute bronchitis.

As the study proceeded the percentage of cases with positive virological findings decreased from 51 in January and 34 in February and March, to 12 in April, and nil in May and June. This fall was associated with and probably due to a rise in the percentage of children in the age-group 0 to 6 months with acute bronchiolitis.

Bacteriological investigation revealed a variety of organisms, many of which are known to be normal inhabitants of the respiratory tract. No relationship was demonstrated between any single bacterium and any one of the clinical groups. Indeed, the isolation rates of a potential pathogen such as *H. influenzae* in croup (2 of 6 cases), acute bronchitis (7 of 37 cases), and acute bronchiolitis (6 of 27 cases) were of the same order as have been obtained in surveys of normal children (Rabe, 1948).

The isolation of only a single culture of *Str. pyogenes* from the cases of upper respiratory infection may have been due to the variety of illnesses included under this term. This relative absence of streptococci in upper respiratory infections was also the experience of Brimblecombe *et al.* (1958).

In 1949 Cunliffe examined a group of children born in hospital and showed that they had a high carrier

rate of coagulase-positive staphylococci. This rate fell until between the ages of 6 months and 2 years it was 20%. More recently Gould and Cruikshank (1957) have obtained coagulase-positive staphylococci from a third of a sample of the normal population. This figure was not exceeded in any of the diseases studied in this investigation.

Special Problem of Acute Bronchiolitis

Failure to obtain evidence for virus infection in acute bronchiolitis has been the experience of other workers, too (Morrison *et al.*, 1957). A number of factors may account for this. All the cases of bronchiolitis were investigated fully, so that the negative findings in this disease were not due to a failure in technique. Perhaps the material for virus isolation was taken from the wrong places; bronchial or bronchiolar secretion obtained by direct aspiration or lung puncture might have been more fruitful but we did not consider such methods justified. In this connexion material from other members of the family with coincident respiratory infections might also have been helpful. Another possibility is that a hitherto unidentified virus is responsible for acute bronchiolitis which may be of the "common cold" variety (Morrison *et al.*, 1957).

In a future investigation it is hoped to explore these possibilities by attempting to culture virus from bronchial aspirations, to add at least one more culture tissue, human amnion, to those previously employed, and to investigate all the family contacts.

It is also possible that viruses are not concerned with acute bronchiolitis and that it is bacterial in origin. Wood *et al.* (1954) have presented evidence that virulent strains of *H. influenzae* are implicated. Our isolation rate of this organism would not appear to confirm this, as the failure to identify virus agents was not matched by any significant increase in the isolation of bacterial pathogens above the number found in other clinical groups. It may be that, as for viruses, the material was taken from the wrong place.

There was no evidence that the time between onset of symptoms and admission was longer in cases of acute bronchiolitis than in other varieties of acute respiratory infection, thus reducing the isolation of viruses. The time of onset was taken as the time at which the infant was last perfectly well, and so included the well-known period of coryza that usually precedes the onset of the severe symptoms.

The inverse relationship between age and number of virus isolations in children with acute bronchiolitis (Table I) raised the problem of whether the failure to identify viruses in this disease was primarily due to the fact that all were 6 months of age or under. Table V shows the low incidence of viruses found in this age-group as compared with older children. If the identification of virus had been limited to serological examination, this might have been explicable on the basis of a failure of antibody production in the first six months of life. The sparsity of positive virus cultures, however, at this age cannot be explained. Thus the problem remains whether acute bronchiolitis is due to an unknown agent or to an agent we were unable to isolate because of difficulties peculiar to this age-group. This is of particular importance because five of the six children in this series who died were aged 6 months or less, four of them dying from acute bronchiolitis.

Croup-associated Virus

It should be noted that this is the first time that croup-associated virus has been reported in the respiratory infections of children in England. Four strains of the virus were isolated and fourfold or greater rising titres of antibodies fixing complement with croup antigen were found in two of these patients; in one there was insufficient serum to test, and the last was negative. A fifth child had a fourfold rising titre but virus was not isolated, possibly because the child had been ill for some days when he was first admitted. Paired sera from his mother, taken at the same time and when she herself was suffering from a "cold," also showed a rising titre of complement-fixing antibodies.

Our isolation of this virus from children with croup confirms the findings of Chanock (1956) and Beale *et al.* (1956, 1958) in their series and of Cramblett (1958) in one case. The isolation of this virus from other types of respiratory diseases, varying from pharyngitis to pneumonia, has not previously been recorded. One further point of note was that one child, from whom croup-associated virus was isolated, not only had a four-fold rising titre of antibodies fixing complement with croup-associated antigen but also had a fourfold rising titre of antibodies fixing complement with Sendai and mumps virus particle antigens. This, too, demonstrates the sharing of antigens in Sendai, mumps, and croup-associated viruses noted by previous workers (Chanock, 1956; Gardner, 1957).

One hundred convalescent sera from children in this investigation were tested against croup-associated antigen and all were negative at a titre of 1/8. Though the numbers are small, it would appear that antibodies to this virus were not commonly present among children in Newcastle at that time.

In our series no viruses similar to Chanock's haemadsorption viruses I or II (now called parainfluenza III or I) were isolated. However, in two cases there was serological evidence of infection with haemadsorption virus II (parainfluenza I or Sendai).

Summary

A clinical, virological, and bacteriological study of 146 children with acute respiratory disease was made in three hospitals in Newcastle upon Tyne during the first six months of 1959.

Except in acute bronchiolitis, evidence of infection by several different viruses was found in each of five clinical categories of illness.

Acute bronchiolitis was remarkable for the complete lack of evidence of virus infection in any of the 27 children. This may have been due to our inability to test secretions from the lower respiratory tract, or to the presence of an unidentified virus. Four of the six deaths were due to this disease.

For the first time in this country croup-associated virus was incriminated in the respiratory infections of childhood. It was associated with clinical illness which varied from mild upper respiratory infection to moderately severe pneumonia.

Bacteriological examination revealed a variety of potential pathogens, but their incidence was of the same order as in normal children.

We are indebted for the help given to us by clinicians, nursing staff, and laboratory technicians, too numerous to mention by name.

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TRIAL OF ADENOVIRUS VACCINE IN ROYAL AIR FORCE RECRUITS

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Several large field trials of adenovirus vaccines in the United States have shown them to be effective against infection with viruses of the same type. Hilleman and his co-workers, using a vaccine prepared from adenovirus types 4 and 7 during an epidemic of infection with these two types, reported that the acute respiratory illness rate was reduced from 23.8% in the control group to 4.8% in the vaccinated group (Hilleman *et al.*, 1956; Stallones *et al.*, 1957). Bell and his co-workers, using vaccine prepared from types 3, 4, and 7, obtained a reduction of 55% in the incidence of febrile respiratory disease when adenovirus type 4 was prevalent (Bell *et al.*, 1956; Gundelfinger *et al.*, 1958). In another trial of a trivalent vaccine, Culver *et al.* (1959) obtained a 43% reduction in the total sickness rate; during this trial also adenovirus type 4 infection was predominant.

In a study of acute respiratory disease in the Royal Air Force, McDonald *et al.* (1958) confirmed that new recruits to the Service had a far higher illness rate than other personnel. This led to a considerable disruption of training programmes. In addition, they found that a substantial number of recruits were discharged from the R.A.F. with serious lung damage before any useful service had been performed. Indeed, the major cause of discharge due to respiratory disease in the R.A.F. was illness acquired at recruit camps. Moreover, they observed the great importance of adenovirus infection as a cause of acute respiratory disease among recruits. This corresponded to findings in the United States (Hilleman, 1958), in Holland (van der Veen and Kok, 1957), in France (Sohier *et al.*, 1957), and in Switzerland (Löffler *et al.*, 1956). Apart from some radical change in the method of accommodating recruits on reception and during training, vaccines appeared to offer the best hope of reducing the problem. A trial of adenovirus type 7 vaccine conducted in the R.A.F. early in 1958 was inconclusive, though the results suggested that it afforded some protection against type 7 infection and possibly protection of a lesser degree against type 4 infection, which was predominant at the time (unpublished results of the Medical Research Council Adenovirus Vaccine Working Party).

Early in 1959, 400 doses of a commercial vaccine containing adenovirus types 3, 4, and 7 (prepared by Parke, Davis & Co.) became available to the R.A.F. at short notice. Clinical trials in the United States had left little doubt about the efficacy of the vaccine, but it was decided to use these doses in a way which might demonstrate their value in this country. They were therefore administered to R.A.F. recruits at Bridgnorth, where a comprehensive survey of acute respiratory disease was already in progress.

Material and Methods

On arrival at Bridgnorth each week recruits are divided into flights of about 70 to 80 men each. The flights are made up of an amalgamation of smaller groups formed at the recruit reception unit as the men arrive; there is some tendency for men who live furthest away to arrive later and so to be grouped together, but no other apparent selection in the composition of groups. Men in each flight sleep, work, and live together during the whole of their two months' training, but they also have contact with members of other flights when off duty. It was decided to offer protection to two incoming flights each week for three weeks during February, 1959, and to compare respiratory infection rates in them with those in three uninoculated flights arriving each week during the same period. In this way it was hoped to demonstrate the value of having a high proportion of protected persons in a flight. The nature of the vaccine and what it was hoped to achieve were explained to the recruits. A total of 402, 91% of the selected flights, volunteered. Of the remainder, some were rejected because they were already ill or appeared to be developing a respiratory illness, and it was thought undesirable to inoculate them.

Inoculation Procedure.—About 70% of the volunteers were inoculated within 24 hours of their arrival at Bridgnorth, and the remainder within 48 hours. A single dose of 1 ml. was injected into the deep subcutaneous tissues of the upper arm, using a separate syringe and needle for each volunteer. All volunteers were inspected 48 hours later for reactions to the inoculation. Local reactions were recorded in 25 men (6.2%); all were mild except for one with a moderate degree of local erythema and induration. A further 10 (2.5%) had mild general reactions, and two had both mild general and mild local reactions.

Recording and Laboratory Procedure

No special records of illnesses occurring in the trial groups were necessary, because in the survey already in progress an illness-record card was completed for every recruit admitted with acute respiratory disease to the station sick-quarters or to hospital until the end of March. Medical officers were asked to take throat swabs for virus-isolation tests, and acute and convalescent samples of blood from as many cases of respiratory illness as possible. During the early part of the trial the proportion from whom specimens were collected was low because of the intensity of the epidemic at the time.

Throat swabs were broken off into 5-ml. bottles containing Hanks's balanced salt solution with 0.5% lactalbumin and sodium bicarbonate; these were transported on solid carbon dioxide to the laboratory at Colindale, where they were stored at −70° C. until tested two to three months later. About three-quarters of them were kept at −10° C. for up to two weeks before being taken to Colindale. Strains of adenovirus were isolated from throat swabs by inoculating each of two tubes of HeLa cell cultures with 0.1 ml. of the transport medium. The cells were maintained in tubes, using Earle's balanced salt solution with 0.5% lactalbumin, 2% horse serum, sodium bicarbonate, and 200 units each of penicillin, streptomycin, and nystatin. Cultures were maintained for 28 days, the medium being changed and passage carried out as necessary. The tissue-culture fluid of cultures showing a cytopathic effect was tested by means of a complement-fixation test against a positive serum. Those which were positive were sent to the Virus Reference Laboratory for typing by means of a neutralization test.

Blood samples were sent to the laboratory by post, where, after separation, the serum was stored at −20° C. until tested. Complement-fixation tests were carried out in cups on plastic plates, using volumes of 0.1 ml. The haemolytic system consisted of a 2% suspension of optimally sensitized sheep red cells together with 2.5 HC_{50} units of complement. The source of complement was guinea-pig serum preserved by the method of Richardson (1941). Antigens were used at their optimal concentration. Sera and antigens were allowed to react in the presence of complement at 4° C. overnight before the haemolytic system was added. Then, after a period of incubation at 37° C., the plates were left at 4° C. to allow remaining red cells to settle before reading. Convalescent-stage sera showing more than 50% fixation in the screening test were titrated in parallel with acute-stage specimens. A fourfold, or greater, rise in titre between paired specimens was regarded as diagnostic of recent infection.

Results

Epidemiological Background.—The incidence of respiratory illness at Bridgnorth was low during the early part of the winter but rose sharply in the week ending January 23, 1959. In early February there was an explosive outbreak with exceptionally high sickness rates; this coincided with the time when the first adenovirus vaccine was being given to new arrivals. The rate of admission to the sick-quarters continued at a high level for four weeks before beginning to fall one week after the last of the inoculations had been given. The number of admissions returned to a low level by the end of March. Evidence obtained from tests on throat swabs and paired specimens of serum from sample illnesses suggested that infection with adenovirus type 3 was occurring throughout this period, but that the main epidemic in early February was probably due mostly to influenza A virus with some influenza B virus infection as well.

Clinical Results

The total number of admissions due to respiratory illness in the protected and in the unprotected flights is shown in Table I. For both groups the illnesses are divided into those in which the onset was on or before the seventh day from the date of inoculation, and those with onset after that time. The seventh day from inoculation was chosen as a time after which the vaccine could be expected to have a protective effect. The admission rate was 36% in the uninoculated flights, compared with 26% for all persons in inoculated flights, whether or not they had been given the vaccine. The difference between these two rates was statistically significant (difference ÷ standard error = 10 ÷ 2.8 = 3.6). The reduction was relatively greater when only illnesses starting more than seven days from injection were considered. The comparable rates of admission were then 20% and 12%, representing a reduction of 40% in the protected flights. The persons who received no

TABLE I.—*Admissions to Sick-quarters with Acute Respiratory Illness (Rate per cent. in Parentheses)*

	No. of Men	All Illnesses	Illnesses within 7 Days of Inoculation	Illnesses More than 7 Days from Inoculation
Unprotected flights	661	236 (36)	106 (16)	130 (20)
Protected ,,	442	113 (26)	58 (13)	55 (12)
Inoculated persons	402	95 (24)	48 (12)	47 (12)
Uninoculated ,,	40	18 (45)	10 (25)	8 (20)
All flights	1,103	349	164	185

TABLE II.—*Adenovirus Isolation Results*

	Illnesses within 7 Days of Inoculation		Illnesses More than 7 Days from Inoculation		Adenovirus Types		
	Tested	Adenovirus Isolated	Tested	Adenovirus Isolated	3	4	7
Unprotected flights	10	0	43	20	18	1	1
Protected ,,	8	0	14	3	2	1	0
Inoculated persons	6	0	12	1	1	0	0
Uninoculated ,,	2	0	2	2	1	1	0
All flights	18	0	57	23	20	2	1

TABLE III.—*Serological Results*

	Illnesses within 7 Days of Inoculation				Illnesses More than 7 Days from Inoculation			
	Tested	Adenovirus	Influenza A	Influenza B	Tested	Adenovirus	Influenza A	Influenza B
Unprotected flights	12	0	7	2	46	16 (2)	1 (1)	4 (1)
Protected ,,	11	3 (2)	5 (3)	2 (1)	17	1	3	1
Inoculated persons	8	3 (2)	4 (3)	1 (1)	14	0	3	1
Uninoculated ,,	3	0	1	1	3	1	0	0
All flights	23	3 (2)	12 (3)	4 (1)	63	17 (2)	4 (1)	5 (1)

Figures in parentheses denote numbers showing a rise in antibody content to more than one antigen.

vaccine in inoculated flights apparently fared worse than those in the totally unprotected flights, but this was probably because some of them were not inoculated as they were already ill. When only those illnesses which occurred more than seven days from the inoculation date are considered, the difference disappears, but the fact that most of their colleagues were inoculated did not appear to protect them from infection.

Laboratory Results

Adenovirus strains were isolated from 23 (31%) of the 75 throat swabs tested (Table II). The isolations were all from men taken ill more than seven days after the date of inoculation. All but three were from persons in unprotected flights, and, of these three, only one came from a man who had been given the vaccine. Of the 23 adenovirus strains isolated, 20 were of type 3, two were type 4, and one was type 7. The strain isolated from the inoculated man belonged to type 3.

The serological findings (Table III) were similar to the isolation results. Of the 86 pairs of serum tested, 20 (23%) showed a fourfold or greater rise in complement-fixing antibody to adenovirus. Only three of these pairs were from inoculated persons, all of whom were ill within the first week after inoculation. Two of the three showed a rise in titre to influenza A as well as to adenovirus, so that the rise in titre to adenovirus may have been in response to the vaccine rather than to natural infection.

The distribution of positive serological tests for influenza A and influenza B is also shown in Table III. Most of the influenza virus infections occurred at, or soon after, arrival at the recruit camp, whereas nearly all the adenovirus infections occurred after the first week. The influenza virus infections were distributed more evenly among the inoculated and uninoculated flights than were the adenovirus infections.

Discussion

The reduction in illness was less impressive than results reported from American trials. This may have been partly due to the fact that many of the respiratory illnesses leading to admission to sick-quarters in both the inoculated and uninoculated were not caused by adenovirus infection. Some of these illnesses were due to influenza virus infection, and in nearly half of those tested no cause was found. A better assessment of the vaccine can probably be obtained by using the virus isolation results from the patients tested to estimate the proportion of illnesses in the two groups due to adenovirus infection.

In the inoculated flights specimens from 14 of the 55 illnesses that occurred more than seven days from injection were tested and adenovirus was isolated from three of them. We may therefore estimate that adenovirus might have been isolated from about 12 patients—that is, $3 \times 55/14$—had specimens from all 55 illnesses been tested. Similarly, in the unprotected flights the number of illnesses from which adenovirus might have been isolated was probably about 60—that is, $20 \times 130/43$. Admission rates due to adenovirus infection, based on these estimates, are 2.7% ($12/442 \times 100$) for the inoculated flights, and 9.1% ($60/661 \times 100$) for the uninoculated flights. These figures represent a reduction in the admission rate of 70%. This is probably a conservative estimate of the protective effect of the vaccine, as only one of the three patients in protected flights from whom virus was isolated had actually received the vaccine.

The value of adenovirus vaccines, previously demonstrated among military recruits in the United States, has thus been confirmed in recruits to the Royal Air Force. Huebner *et al.* (1955) gave a type 3 vaccine to volunteers, and showed that it induced neutralizing antibodies and protected against challenge with virus of the same type. There has been no previous report, however, of the efficacy of a vaccine against type 3 infection under natural conditions.

Summary

A limited supply of commercially prepared trivalent adenovirus vaccine containing strains of types 3, 4, and 7 was administered to 402 R.A.F. recruits to test its value. Two out of five flights of recruits arriving at Bridgnorth each week for three weeks during February, 1959, were inoculated.

Influenza A, influenza B, and adenovirus infections were all highly prevalent at the time the injections were given and during the weeks that followed. The adenovirus strains isolated were predominantly type 3.

There was a total reduction of 40% in the admission rate for acute respiratory illness occurring in the inoculated flights more than one week from inoculation. The protective effect of the vaccine against adenovirus infection, estimated from virus isolation results, was 70%.

We are indebted to the staff of the Station Sick Quarters at R.A.F., Bridgnorth, for their help with records and collection of specimens; to Dr. M. S. Pereira for typing the adenovirus strains; and to Mr. G. V. Heimer and Sergeant C. Woodward for their technical assistance. Acknowledgment is also made to the Director-General of Medical Services, Royal Air Force, for permission to publish results.

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The level of natural radiation from the rocks varies in different parts of the world. The collection of information about its effects in man from those areas where its level is exceptionally high was recommended by the W.H.O. Committee on Radiation in 1958. The committee's report was previously issued in mimeographed form (W.H.O./Rad/5) and is now published as No. 166 in the W.H.O.'s Technical Report Series. Briefly, it recommends that a study be carried out in Kerala, South India. There a relatively stable population of about 80,000 is exposed to natural radiation that is "10–15 times that normally encountered." The report is available from H.M.S.O. for 1s. 9d.

PSYCHOTHERAPY IN MIGRAINE

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In a neurological out-patient department a number of patients complaining of migrainous headaches unassociated with physical disease show little or no response to drugs and tend to become regular attenders. Dissatisfied with this frustrating situation, we decided on a combined approach to ascertain, firstly, to what extent, if any, psychological factors were playing a part; and, secondly, the value of treatment on psychotherapeutic lines. Patients were examined for the presence of physical conditions usually held to precipitate or aggravate migraine; after which they were investigated and treated psychiatrically. Here we present observations and results on 35 patients followed up for a period of 6 to 12 months.

Materials and Methods

The diagnosis of migraine was made when patients complained of paroxysmal headaches, usually unilateral, associated with nausea and vomiting, often preceded by visual disturbances and, less commonly, by other focal symptoms, and followed by a period of exhaustion. All patients had been referred for specialist advice because attacks were persisting or becoming increasingly severe, causing incapacity for work and emotional disturbance, despite standard migraine treatments in various combinations and doses. Only patients with a history longer than two years were included, in order to provide an adequate background against which both severity and results could be assessed. Other patients excluded were those with suspected cerebral tumour or angioma and those with severe hypertension, as well as patients with obvious psychogenic headaches without the characteristics of migraine.

Eight patients fulfilled all conditions but did not complete the minimum period of follow-up and are omitted from the series. Two of them were seen only once; one, a schizophrenic, was shortly afterwards admitted to a mental hospital; the other a boy of 12, whose anxious mother had taken him to a number of other hospitals. Two patients left London, four stopped attending after two to three months, one had previously been to a mental hospital, and one lived under severe domestic strain. The other two, one of whom was taking pethidine regularly, were reluctant to accept any treatment other than continuation of large quantities of drugs to which they had been accustomed.

The following procedure was adopted. First, a full formal history, with special reference to headache, associated symptoms, drug habits, and social and domestic circumstances, was taken, followed by a general and neurological examination. Particular attention was paid to evidence of disease of the nervous system, refractive errors, sinus infection, allergic disorders, gastro-intestinal disturbances, cardiovascular disease, and endocrine abnormalities. All patients had their urine analysed and plain radiographs of the skull were taken; other investigations were done where necessary—for example, blood count, E.S.R., Wassermann reaction, blood urea, etc.—or patients were referred to special departments such as E.E.G. and E.N.T. Patients were then seen psychiatrically, and subsequently were followed at monthly or six-weekly intervals by both of us. We gave no physical treatment, and though patients were not made to stop drugs they were already taking they were advised to reduce them to a minimum.

Of the 35 patients, 20 were women and 15 men; their ages ranged from 21 to 59. Sixteen women were housewives, eight were in part-time or full-time employment varying from charwoman to model; and four were unmarried whole-time workers—a factory worker, a clerk, a civil servant, and a dietitian. The occupations of the men varied from unskilled labourer to manager of a large manufacturing concern.

History

Twelve women and six men gave a history of migrainous headaches in a parent or sibling. Two women and two men gave a history of mental illness in a parent. The father of one woman committed suicide; she herself had received mental-hospital treatment for depression, was married to a transvestite, and had a backward child. One man had a mongol child.

Their previous histories of physical diseases were without significance. Apart from childhood ailments two women had had a hysterectomy, one a thyroidectomy, two toxaemia of pregnancy, one nephritis, one typhoid, one a prolapsed lumbar intervertebral disk; two men had had tuberculosis. Three patients gave a history of head injury; in two this was mild, and in the one in which it was moderately severe it preceded the onset of migraine by 15 years.

In their previous psychiatric history four women had had a depressive illness necessitating treatment; six volunteered that they had always been "nervy," anxious, easily upset, and inclined to worry excessively; and one had a persistent facial hemispasm after a bomb incident. Of the men, four were self-confessed "nervous types," one had a compensation neurosis, and one a history of bouts of excessive drinking.

Associated Physical Conditions

In all cases careful inquiry was made for possible physical factors causing or aggravating headaches. No patient had associated epilepsy. Electroencephalography was performed on eight patients: in four the record was normal; in one doubtfully abnormal; two had a mild generalized non-specific abnormality; and one had doubtfully lateralizing features which had remained unchanged for three years.

Ocular Abnormalities.—Of the 35 patients, 25 had had their eyes tested and 14 wore spectacles. None had ocular disease and none noticed any improvement in migraine from correction of refractive errors.

Diseases of Ear, Nose, and Throat.—Two patients gave a history of chronic sinus trouble, one of whom had had operative treatment; both thought it unrelated to their headaches. Two other patients were found to have infection of the maxillary or frontal sinus causing mild symptoms unrelated to their migraine. In one patient the chance finding of a small osteoma in a frontal sinus was thought to be incidental.

Allergy.—Two patients gave a history of allergic disorders before the onset of migraine. None had evidence of allergic skin diseases, rhinitis, or asthma at the time of examination.

Gastro-intestinal Abnormalities.—One man had occasional diarrhoea as a result of recurrent dysentery but noticed no relation with his migraine; one had a history of alternating dyspepsia and migraine, and subsequently developed a gastric ulcer with relief of migraine; another had recurrent bouts of dyspepsia unrelated to migraine without radiological abnormality. Most patients reported anorexia and gastric upsets with their headaches. None noticed that migraine followed any particular article of diet.

Cardiovascular Disease.—Mild hypertension without cardiovascular hypertrophy was found in two patients and was regarded as incidental. As stated before, patients with severe hypertension with sustained diastolic pressures of 120 mm. Hg were excluded. One man had developed angina of effort after many years of migraine.

Endocrine Disturbance.—No patient had evidence of major endocrine upset.

Other Conditions.—Two patients had a mild anaemia, one chronic bronchitis, and one cervical spondylosis.

Duration of Migraine

Many patients had had headaches which in the course of time became more severe and assumed the characteristics of migraine; in them the transition from one to the other was hard to establish precisely, as was the exact year of onset in patients with a long history. Some of the following figures are therefore only approximations.

The duration of migraine varied from 3 to 37 years, with an average of 11½ years. Of the women, four had had migraine for five years or less; 10 for 6–10 years; two for 11–15 years; and one each for 18, 20, 30, and 37 years. Nine women had a history of headaches or bilious attacks in childhood followed by an interval of freedom before migraine developed. Most gave a history of insidious onset with gradually increasing severity and frequency. Only in two was the onset sudden. Six men had had migraine for five years or less; five for 6–10 years; and one each for 11, 16, 17, and 18 years. Only one man gave a history of having suffered from headaches in childhood which gradually became migrainous; one had headaches in his twenties, which ceased, only to begin again as migraine in his fifties; and two gave a history of sudden onset. Table I gives the age at onset in relation to presenting age.

TABLE I.—*Age at Onset in Relation to Presenting Age*

Age	Number of Patients			
	Age at Onset		Presenting Age	
	F.	M.	F.	M.
11–20	7	5	—	—
21–30	7	4	4	4
31–40	4	4	7	8
41–50	1	1	7	1
51+	1	1	2	2
	20	15	20	15

Features of the Attack

All 35 patients gave a history of paroxysmal headache, frequently unilateral but not confined to one or other side. All complained of nausea; some vomited with most attacks, some only rarely. Fourteen had at one time or another characteristic visual disturbances; four had focal disturbances—two of speech and two face and limb paraesthesiae. Other common symptoms were malaise, dizziness or muzziness, inability to concentrate, insomnia, etc. All patients were having at least one attack a week, many two or three or even more.

The duration of headache varied from an hour to several days; or they might follow in quick succession without interruption for weeks. Between attacks many complained of daily or even continuous headache and heaviness of the head or other anomalous and at times bizarre sensations. Often headaches which were migrainous at onset persisted as indefinite and dull pains, equally distressing because of their duration. Patients who were well between infrequent and isolated attacks were not seen in this series.

Of the 13 women who had borne children, nine were free from attacks during pregnancy. Two women had migraine mostly with periods; while four noted occasionally that they were worse at this time, and one that she was better. There was no clear relation to the menopause. Of the five women past the menopause one was improved, three were unchanged, and one was worse.

Incapacity

An attempt was made to assess to what extent patients were incapacitated (Table II). All patients were disabled at the height of the attacks and many for a day or two after; some were continuously impaired in varying degrees between attacks.

TABLE II.—*Incapacity*

Degree of Incapacity	F.	M.
Impaired efficiency during attacks	6	7
Up to 24 hours a month in bed or off work	4	6
1–3 days ,, ,, ,, ,, ,, ,, ,,	3	—
4–6 ,, ,, ,, ,, ,, ,, ,,	3	1
Total incapacity; had to give up work	4	1

A greater number of women took time off work or, in the case of housewives, spent days in bed. The only man who had not worked for two years because of migraine had had a bad attendance record in previous years and also suffered from a compensation neurosis. Two men gave up working overtime, with consequent financial hardship. One classed under "impaired efficiency" occasionally took a week off work; another changed jobs frequently in the hope of finding one more suitable to his migraine. All four women who gave up work were married; one had not worked for eight years, though childless and keen to occupy herself; a mother of two children gave up a responsible supervisor's post two years previously because of chronic invalidism but restarted part-time work while under our care; another gave up a trying secretarial post in the City but recommenced similar employment in the suburbs, also under our care. One woman classed as taking two or three days off work a month had a spell of three months continuously off work the preceding year; one classed under "impaired efficiency" had occasionally to spend a week in bed. Two of the women who had to have four to six days off work every month were unmarried; they were, respectively, a clerk and a civil servant. Most wives gave a history of their husbands having to do the housework during attacks.

In summary, five patients had to give up work; 17 lost an aggregate of over 400 working days a year, an

average of nearly 25 days each; and 13 patients lost no time, but their efficiency was impaired during attacks.

Previous Treatment

All patients had received prolonged treatment with aspirin, codeine, barbiturates, and other analgesics, and all but three had had various ergot preparations singly or in combination. Three patients had received regular pethidine by mouth or injection, three antihistamine drugs, three had had hormone treatments, and two had had carbachol. In addition, three had attended a private migraine clinic for hormone and other drugs by injection, one attended a private school of relaxation, and one had had injection and later section of a supra-orbital nerve. Other drugs given were "theobromine," amphetamines, and tranquillizers. Not infrequently the vehicle of administration of drugs was a suppository. This list is not exhaustive, because some patients had received drugs without being told either their name or nature.

Fifteen patients had previously been to 30 hospitals for their headaches. All had received medication for attacks as well as regular prophylactic medication in between. In some patients this had led to a drug habit. For example, one woman was taking daily at least 12 gr. (0.78 g.) of amylobarbitone sodium, 6–10 codeine co. tablets, 2–8 tablets of a proprietary ergot preparation, a proprietary ergot preparation by injection every two or three days, and at times other analgesic and tranquillizing drugs.

A number of patients were found to be obtaining drugs from more than one source—for example, from various chemists, doctors, and hospitals—with the result that no one doctor knew exactly what they were taking. Most patients thought large doses of drugs were having little or no effect but were afraid to stop them. Those who complained of severe persistent headache, depression, insomnia with drowsiness by day, inability to concentrate, poor memory, lack of energy, and lack of appetite, were often found to be taking large quantities of drugs. These patients also appeared to run from one attack of migraine to another without an intervening period of well-being.

Psychiatric Investigation

All patients were told that they were going to see a psychiatrist. Some were glad of the opportunity of talking about themselves and their troubles. Others, however, were upset because they took this to mean that the neurologist considered them psychiatric cases, with the result that initially they were on the defensive and tended to minimize or deny possible sources of emotional difficulties. In retrospect this difficulty could have been avoided had patients merely been told they were being referred to another doctor.

The psychiatrist's task was, however, made much easier, as formal histories had already been obtained and organic conditions excluded. Nevertheless another detailed history of migraine was taken, paying special attention to onset and times of exacerbation. This was followed by a detailed personal history, again paying special regard to dates and correlating exacerbations of migraine with disturbances in the patient's life. In this way attacks of migraine were gradually linked with emotional difficulties or upsets. Most patients had been unaware of any association even when it seemed obvious to them in retrospect, and certainly could not have related them before the psychotherapeutic interview.

Patients were then invited to talk about themselves freely with only such questions as "Tell me about your headaches" or "Tell me about yourself," the psychiatrist allowing the interview to be led by the patient. When it became clear that certain events or certain persons were associated with exacerbations, the patients were led back to discuss these and their emotional reactions either later in the same interview or as the starting-point of subsequent interviews. Most patients were seen two or three times in the first month for interviews lasting up to 45 minutes; psychotherapy was then continued at monthly or six-weekly follow-up visits. Some patients who at the first interview seemed trouble-free later came out with unsuspected troubles and difficulties. These also would not have been elucidated by direct questioning, since they had answered such questions as "Have you any worries?" at the first interview in the negative.

All gave the impression of having some disturbance or unhappiness in their lives. Since little would be gained by attaching formal diagnostic labels, it was thought simpler and more informative to grade patients by an assessment of degree of psychiatric disturbance. They were accordingly grouped into three categories: mild, moderate, and severe (see Table III). Those classed as mildly disturbed were primarily worried about their migraine; those moderately disturbed were, in addition, anxious and depressed to a significant degree; those severely disturbed were agitated, were depressed, and had suicidal thoughts.

TABLE III.—*Degree of Psychiatric Disturbance*

Sex	Mild	Moderate	Severe
Women	8	9	3
Men	6	9	—
Total ..	14	18	3

It is noteworthy that the three patients classed as severely disturbed were women. One of them had had previous psychiatric treatment for depression. All had ample psychiatric symptomatology which would have made them urgent cases for psychiatric treatment had they not been referred because of their presenting symptom, headache.

All patients were asked what they thought their headache was due to, or what illness they were afraid they might have and what they thought might happen if they were not relieved. A number thought at one time or another that they had serious disease, but fear of this had faded as time passed and they remained well apart from migraine. Of the 14 mildly disturbed patients, seven attributed their headache to migraine; four to "nerves"; one to overwork; one to "worry, constipation, or excessive reading"; and one to an "inferiority complex." Of the 18 moderately disturbed patients, only three thought it was due to migraine; three thought it was due to "nerves"; one to catarrh; one wondered whether he was going mad; another really thought he had damaged his brain by exceeding his mental capacity; three did not know, and the others were afraid they might have a "tumour," "cancer," "clot," or "cyst on the brain." All three seriously disturbed women thought they were going mad, and one also wondered whether her brain had been affected by atomic radiation. None had a conviction of disease amounting to a delusion. It seems, therefore, that as the degree of psychiatric disturbance mounted the more serious was the disease patients thought they had.

Psychological Factors

During the course of the investigation it became apparent that psychological factors or emotional disturbance could influence the frequency and severity of migraine in three different ways.

In some patients the first attack followed an emotionally upsetting situation. In one woman this was the anniversary of her father's suicide by shooting himself through the head; another lost her father, sister, and uncle within a few months; in another the noise made by a fellow worker at her factory bench persisted in the patient's head and gradually developed into migraine. In one man the first migraine developed during a family crisis at the same time as he had to give up his life's ambition of a stage career.

Much more common was the finding of emotional difficulties as the background to persistent aggravation of already existing migraine. All the 16 married women had some domestic trouble which upset them. The patient whose husband was a transvestite and who had a backward child has already been mentioned; another was unhappy because her husband was on permanent night duty and left her with the management of a difficult son; the husband of another had chronic heart disease with temperamental changes; one husband was a sailor away for months at a time; one frankly said it was her husband who ought to see the psychiatrist; one was an unsettled foreign girl married to a British soldier. Of the four unmarried women, two had always been shy and nervous, while two were frankly dissatisfied spinsters. Much the same circumstances were found among the men, with the addition of disappointments or annoyances at work.

In this connexion it is of interest that in a number of our patients, mostly men, attacks of migraine occurred only at week-ends while they were at home. One man described how his headaches had originally begun in this manner, then developed also when he went to the cinema or on long drives with his wife, and thereafter occurred nightly but always cleared up in the morning by the time he reached his office. This tallies with the experience of two other patients who to their surprise were free from attacks during the war. One was a woman whose husband served abroad throughout; and the other a married man who was free from headaches for the five years he was an officer in a fighting regiment.

The third way in which psychological factors seemed to act was that in established migrainous subjects they precipitated a series of attacks. This was more obvious among the men. One developed an exacerbation when told his child was a mongol; another when he was rejected for the Services; a third during a period of excessive work for his trade union; another in relation to accountancy examinations; another during his wife's pregnancy; and a childless woman when she lost her pet dog. One patient described it graphically: "My mother died, my daughter went to Canada, my husband lost his teeth, and my boy changed to ladies' hairdressing, all in one month."

At least two-thirds of the patients volunteered that their migraine was made worse by worry, fright, annoyance, rows, or other upsets; some said excessive work or "too much thinking" brought on attacks. Holidays and festive seasons sometimes had the same effect. Some developed exacerbations when they heard of serious illness or death in a friend or relative and were then inclined to think they had similar trouble. This led to a number of recurrences after an initial period of improvement. Anniversary times seemed to play a part in some exacerbations: three patients attended 10 years after they had lost a favourite parent, and three who were unhappily married had been so for 10 years. In four of these six the anniversary coincided not only with the year but also the month and almost the day of attendance.

In several patients with a positive family history it seemed that their migraine might not have been hereditary but rather acquired through early imitation or identification with a sufferer close to them.

Intelligence and Personality

The intelligence of our patients, roughly assessed, varied as widely as their occupations and bore no relation to severity of migraine. Though anxiety and depression were common, obsessional features seemed no more apparent than in any other group of patients. A few of our patients laboured under disappointed hopes or thwarted ambitions, but, if anything, attacks seemed related to unhappiness and annoyance in their emotional relations rather than to result from disturbing or faulty personality factors in their make-up.

Results of Treatment

The natural history of migraine, with its variations and the many unaccountable factors by which it may be influenced, makes assessment of results of the treatment difficult. We therefore avoid the word "cure," particularly as it became clear during the course of this work that some patients remained liable to relapse as the result of an untoward event, though they became less susceptible and tended to get over exacerbations more easily and quickly. In order to minimize observer error and therapeutic bias, both regarding migraine and psychiatric disturbance, we assessed all patients independently. Allowance was also made for the fact that some patients may desire to please the doctor by minimizing symptoms, while others are reluctant to admit improvement when this occurs in the absence of any physical therapies.

Assessment of improvement of migraine was based on frequency, severity, and duration of headache, incidence of vomiting and visual disturbance, degree of incapacity during attacks, and diminution of drug intake. The assessment of psychiatric improvement was based on lessening or disappearance of anxiety and depression. In each of these aspects improvement was assessed as no change, mild to moderate, and marked. In 80% of patients our assessments agreed, while in the remainder our differences were slight and evened out. Our aim was limited to helping patients sufficiently to lead normal lives in which they could endure infrequent headaches without incapacity, without becoming anxious or depressed, without interval medication, and only minimal, if any, medication during attacks.

TABLE IV.—*Results of Treatment*

Improvement	Migraine	Psychiatric	Drug Reduction
Unchanged	2	5	1
Mild-moderate ..	16	15	15
Marked	17	15	19

Table IV shows that in 94% there was a significant improvement in migraine, in 86% in psychiatric disturbance, and in 97% a significant reduction of drug intake.

"Mild-moderate" improvement of migraine meant that attacks were reduced in frequency and severity up to four a month, causing little distress, with freedom between and improved working capacity. Those markedly improved still had occasional migraine—never more than once or twice a month—which was milder, of shorter duration, and had little or no effect on working capacity; there were also prolonged periods of freedom in which they were well.

Improvement was further assessed by recording the drugs that patients were taking before and after attending. In Table IV the group labelled "mild-moderate reduction in drugs" mostly stopped taking tablets to prevent headaches but continued much the same medication for attacks; as these, however, had diminished both in frequency and in severity they were, in fact, taking fewer tablets than before. A "marked" reduction meant that patients were taking no medication between attacks and only a little aspirin, codeine, or ergotamine during them. A few were able to stop all tablets. The most impressive feature was the overall reduction of interval medication. No relation was observed between duration of migraine and therapeutic result.

Six patients relapsed after initial improvement, in each case after an identifiable distressing event, and improved again later. Eighteen patients remain under two to three monthly observation and have now attended for 18 to 24 months.

Discussion

Though unselected for the National Hospital, these patients were naturally selected by having been referred to a specialist centre because they were severely incapacitated by frequent attacks uncontrolled by the standard drug treatments or because they were severely disturbed by their attacks. They cannot, therefore, be considered representative of the migraine population as a whole.

The common organic diseases alleged to aggravate or even cause migraine were so infrequent as to suggest that they were incidental. On the other hand, all our patients showed evidence of psychiatric disturbance and many appear to have been helped by simple psychotherapy. Though it is usually assumed that psychiatric illness associated with migraine is due to the migraine, and therefore to cure the migraine is to eliminate the psychiatric disturbance, our results show the reverse—namely, that frequency and severity of attacks may be influenced for better or for worse by psychological factors. It seems almost as if it was more important to ask patients "Who or what is your headache?" rather than "When or where?" Improvement was not related to new or additional drugs, since none were given; indeed, the best results were obtained in those who finally took minimal or no drugs at all, even during attacks. Patients reduced drugs partly on our advice, and partly as they noticed improvement. It appeared that excess drugs were making some patients worse, since all who said they were never entirely free from headache as well as having frequent migraine were in fact taking large quantities. In some patients drug-taking had become a habit, even to the point of addiction, and migrainous symptoms became mixed up with the side-effects of drugs. In many patients a reduction in total drug intake resulted in drugs that had ceased to control migraine attacks regaining their earlier therapeutic effect.

Results of psychotherapy must be assessed against the beneficial effect resulting from the mere fact of visiting a hospital, giving a detailed history, being fully examined, and having fears of serious illness allayed. In addition the interest shown by two doctors concurrently and repeatedly doubtless played a part. In five cases improvement seemed to be related to events in the patients' lives unconnected with our endeavours. For instance, one patient's husband developed a mediastinal tumour; another's mother-in-law died suddenly. Both reported these facts and improvement at the same interview. The third patient improved when rejected by an Army Medical Board; the fourth on becoming pregnant; and the fifth when he developed a gastric ulcer. Another patient improved because, as he said, he realized that there could be nothing the matter with him because we were not giving him any treatment, so there was no need for him to have headaches.

Even those patients classed as not improved ceased to deteriorate, nor did drug intake increase or migraine incapacity become worse. In a few patients it was felt that no major improvement could be expected until they had relinquished their drug habits. Two patients could not be helped.

Summary

A group of 35 patients suffering from migraine in whom standard remedies had failed were studied physically and psychiatrically and treated by psychotherapy. Followed up at 6–12 months, the majority had improved, with reduction of headaches, psychiatric disturbance, drug intake, and incapacity.

It is concluded that in this group of migraine patients psychological or emotional factors played an important part in aggravating the frequency and severity of attacks.

We thank the physicians of the National Hospital, Queen Square, for access to case notes and permission to publish.

The National Library of Medicine possesses a draft of a letter by John Shaw Billings, dated August 26, 1887, to the Boston sculptor, Truman H. Bartlett. Mr. Bartlett was extremely interested in the relationship between Abraham Lincoln's physical characteristics and his mental and moral powers, and in the summer of 1887 he requested Billings' opinion on the matter. Billings points out that "one of the characteristics of Mr. Lincoln's physical structure was the small proportion of the vascular and glandular systems, including the blood vessels and lymphatics, as compared with the bones and muscles." His metabolism, Billings added, was slow, but he believed that such considerations covered "but a very small part of Mr. Lincoln's characteristics. There are thousands of men in this country whose ancestry and early surroundings were similar to his, whose immediate ancestors had been exposed to malarial influences—whose food had been fried pork, saleratus bread, etc., and who are the tougher survivors of this sort of bringing up, and who are tall, lean, sallow, with harsh, dry skins, etc. . . ." W. H. Herndon, replying to another letter from Bartlett on the same subject, terms the "pork and miasmatic" theories guesswork; he calls physicians theoretical above all classes of men, refuses to surrender facts for theories, and maintains that Lincoln "had a fine network of nerve under the coarse flesh." (*U.S. National Library of Medicine News*, February, 1960.)

CARBUTAMIDE IN DIABETES

REPORT OF A LONG-TERM TRIAL, WITH SPECIAL REFERENCE TO LATE FAILURES

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Since the introduction of oral treatment of diabetes in 1955 (Bertram, Bendfeldt, and Otto, 1955; Franke and Fuchs, 1955), research work in this field has rapidly increased and over 1,000 papers on the subject have been published. Nevertheless, the mechanism of action of the compounds used is still a subject of controversy. The reported results of long-term treatment have shown great variations, probably because of lack of uniformity in the indications for oral treatment and in the criteria used to assess benefit. In addition, the period of treatment has usually been relatively short, which makes the evaluation of late results difficult.

Some early reports drew attention to failure of treatment after prolonged administration (Heinsen and Hagen, 1956; Engelhard, 1956; Brechman, 1957; Otto, 1957; Mohnike *et al.*, 1957; Pfeiffer *et al.*, 1957; Dotevall, 1958). These so-called late failures have often been attributed to neglect of the diet, unsuitability of the patient for oral treatment, infections (Bertram, 1958), or similar causes. Other authors have referred to the possibility of the beta cells failing to function after prolonged oral therapy (Pfeiffer, 1957) and lack of response due to the development of tachyphylaxis against the drug (Heinsen and Hagen, 1956).

In the present investigation, special attention has been paid to the results of long-term therapy. Oral antidiabetic therapy was instituted in this hospital in the autumn of 1955. Thus at the time this report was written some of our patients had received this treatment for over three years.

Material and Methods

The series consisted of 270 patients whose treatment with carbutamide (N-butyl-N-sulphanilylurea, "BZ55") was begun during the period November, 1955, to January, 1957—that is, 28–42 months before the end of the follow-up time. In conformity with the generally approved principles, oral treatment was instituted in middle-aged or elderly patients in whom diet alone did not adequately control the diabetes and in insulin-treated patients whose insulin requirements were not high.

In most cases the treatment was begun at the hospital, and the patient was instructed about the necessity of maintaining a strict diet. The dosage was 2.5 g. on the first day, 2 g. on the second day, 1.5 g. on the third day, and thereafter according to the individual needs of the patient. If necessary it was increased later up to 2–2.5 g. a day. After discharge from the hospital all the patients were examined in the out-patient department at intervals of one to three months.

The criteria used in assessing the results of treatment were improvement in the patient's general condition, gain in weight, disappearance of thirst and polyuria, and non-appearance of complications of diabetes. The laboratory tests carried out were estimations of the blood-sugar, urine-sugar, and urine-protein values, and tests for ketosis. Since most of the patients were regularly employed outside their homes and the collection of 24-hour urine specimens was therefore not possible during working hours, the determination of sugar in urine had to be made from as much of the 24-hour specimen as was available. This method does not give a fully correct picture of the urinary excretion of sugar during 24 hours, but together with the blood-sugar determination it may be regarded as a satisfactory indication of the effectiveness of control of the disease.

Differential blood counts and liver-function tests were at first carried out monthly, but later at longer intervals.

The treatment was regarded as successful if, in addition to improvement in the clinical signs, the fasting blood-sugar in the morning was below 200 mg./100 ml. (Hagedorn) and the sugar content of the urine below 1%, corresponding to an average 24-hour excretion of about 10–15 g. of sugar. Transient increases above these values were not taken into consideration. If the fasting blood-sugar value persisted at over 200 mg./100 ml. or the urine sugar at over 1% despite increase of the carbutamide dosage up to 2–2.5 g. a day, treatment was regarded as having failed.

Patients whose treatment was successful during the first month, and later proved a failure, have been classified under "late failures." To clarify the part played by possible dietetic errors, the late failures were usually admitted to hospital for two to three weeks for observation, and carbutamide was continued in the same dose as before.

Results in Patients Previously under Dietetic Treatment Only

Of the 262 diabetic patients in this series, 148 had been treated by dietetic restrictions only. Primary failure during the first month occurred in 27 of these cases (18% of the group). Among the cases that at first were successful, there were 46 late failures (37% of the originally successful cases) (Table I). From 12 to 27% of the patients treated became "late failures" in each yearly period of observation. The number of late failures was relatively largest among the younger patients, being 80% among those who were 30–39 years of age at the onset of diabetes and 60% in those who were 40–49 years. Late failures were fewer among those who were older when the disease began, being

TABLE I.—*Distribution of Late Failures by Age at Onset of Diabetes and Duration of Oral Treatment. Patients Previously Treated by Dietetic Means Only. Failures/Patients During Corresponding Period*

Age at Onset of Diabetes	Duration in Years of Oral Treatment				Late Failures	
Years	<1	1–	2–	3–4	Total No.	%
30–39 ..	2/5	2/3	0/1	0 0	4/5	80
40–49 ..	3/10	2/6	1/4	0 1	6/10	60
50–59 ..	5/40	4/22	1/12	2 7	12/40	30
60–69 ..	9/49	6/35	2/27	2/7	19/49	39
70–79 ..	1/15	2/11	2/7	0/0	5/15	33
80– ..	0/2	0 1	0/1	0 0	0/2	0
Total ..	20/121	16/78	6/52	4/15	46/121	37
Percentage	17	21	12	27		

34% in those over 50 years of age at the time of onset of diabetes. But even in this group late failures occurred, even after successful treatment for one to two years with normal blood-sugar values (under 120 mg./100 ml.) and sugar-free urine.

During the period of observation the number of patients under treatment declined somewhat, because of deaths or transfer elsewhere for treatment.

A definite correlation could not be observed between the number of late failures and the duration of the disease before the beginning of oral therapy (Table II).

TABLE II.—*Distribution of Late Failures by Duration of Diabetes and Oral Treatment. Patients Previously Treated by Dietetic Means Only. Failures/Patients During Corresponding Period*

Duration of Diabetes	Duration in Years of Oral Treatment				Late Failures	
	<1	1–	2–	3–4	Total No.	%
Under 1 year	9/57	5/41	1/26	2/6	17/57	30
1–4 years	8/39	7/20	3/15	1/5	19/39	49
5–10 ,,	3/20	3/12	1/9	1/4	8/20	40
Over 10 yrs.	0/5	1/5	1/2	0/0	2/5	40

In cases with a history of diabetes of less than one year's duration the late-failure rate was 30%, in those with a history of one to four years 49%, and in those with a longer history 40%.

Results in Patients Previously Treated with Insulin

The number of cases treated previously with insulin was 114. Primary failure during the first month of carbutamide therapy occurred in 56%. There were also more late failures (50%) in this group of patients than in the group which had previously had diabetic treatment only. Late failure was not clearly related to the age at onset of diabetes in the patients previously treated with insulin (Table III). It is true that both

TABLE III.—*Distribution of Late Failures by Age at Onset of Diabetes and Duration of Oral Treatment. Patients Treated Earlier with Insulin. Failures/Patients During Corresponding Period*

Age at Onset of Diabetes	Duration in Years of Oral Treatment				Late Failures	
	<1	1–	2–	3–4	Total No.	%
30–39 years	2/2	0/0	0/0	0/0	2/2	100
40–49 ,,	2/6	1/3	0/1	0/1	3/6	50
50–59 ,,	4/14	1/6	1/4	2/2	8/14	57
60–69 ,,	3/15	1/10	1/8	0/4	5/15	33
70–79 ,,	6/13	1/5	0/2	0/1	7/13	54
Total ..	17/50	4/24	2/15	2/8	25/50	50
Percentage	34	17	13	25		

of those who were under 40 years of age and 50% of those who were 40–49 at the time of onset were failures; but the number of patients in these subgroups was very small and therefore assessment in terms of percentages has little significance. Of those aged 50–59 at onset 57% were late failures and of those aged 70–79 at onset 54% were late failures. The proportion of late failures occurring during each yearly period of observation varied from 13 to 34%.

The influence of the duration of the disease on the late-failure rate was apparent in this group (Table IV). In those with diabetes for less than one year, the late-failure rate was 29% among the originally successful cases. The rate was much higher (50–67%) among those with a longer history of the disease.

TABLE IV.—*Distribution of Late Failures by Duration of Diabetes and Oral Treatment. Patients Treated Earlier by Insulin. Failures/Patients During Corresponding Period*

Duration of Diabetes	Duration in Years of Oral Treatment				Late Failures	
	<1	1–	2–	3–4	Total No.	%
Under 1 year	2/7	0/4	0/3	0/0	2/7	29
1–4 years	5/19	3/10	1/7	1/6	10/19	53
5–10 ,,	6/18	1/10	1/5	1/2	9/18	50
Over 10 yrs.	4/6	0/0	0/0	0/0	4/6	67

The average insulin requirement of the patients who became late failures remained approximately the same as before the oral treatment was begun, being approximately 42 units/24 hours before oral treatment and approximately 43 units after its discontinuation. The required dosage of insulin was greater after the treatment in four cases but was less in three cases. The average pre-treatment dose of insulin in cases of late failure was higher (42 units) than that of the patients whose oral treatment continued to be successful (28 units).

Observations on Late Failures

The sex distribution was the same among the late failures and in the group whose disease remained successfully controlled by carbutamide. The difference in the mean blood-pressure values in these two groups was not statistically significant.

Ketosis appeared to be present before the commencement of oral therapy in a larger proportion of the cases that were failures. However, in 12 of the remaining successful cases there also had been ketosis before oral therapy began.

Albuminuria developed during oral therapy in five successful cases and disappeared in one case.

A diagnosis of peripheral neuritis was made in one patient during oral therapy. The onset or increase of retinopathy was not observed during successful treatment in the 35 cases whose fundi were examined before and during treatment.

Late failure due to dietetic error occurred in one case only. This patient's condition improved with strict dieting during his stay in hospital, enabling oral treatment to be continued. In the other cases of failure a controlled diabetic diet in the hospital could not restore the blood-sugar to a level that would have permitted continuation of oral therapy. Increasing the dosage of carbutamide as the blood sugar rose merely postponed the time of ultimate failure by one to six months.

The insulin requirements of the patients previously treated by a diabetic diet were in the range of 20–40 units/24 hours after late failure. In 10 cases of late failure a new attempt at oral treatment of diabetes was made after 1 to 12 months' insulin treatment: in eight of these it was possible to keep up the treatment with success, in some for as long as four months, but an estimation of the permanence of the results is not yet possible.

Dermatitis occurred as a side-effect of treatment in 14 patients (5.2% of the total series). In two patients it developed immediately after the first doses, in nine during the first months, and in three at a later stage. Treatment had to be discontinued in seven cases, but in the others its continuance was possible after a short interval. No changes were observed in the differential

blood counts and liver-function tests during the three years of oral treatment of diabetes.

Discussion

The percentage of late failures with oral antidiabetic therapy ranges from 4 to 20 in different reports (Brechmann, 1957; Mohnike *et al.*, 1957; Pfeiffer *et al.*, 1957; Dotevall, 1958). Evidently the principal reasons for this are differences in the indications for oral therapy and in the criteria of successful treatment. The principle that oral antidiabetic therapy should be instituted only when control of the disease by diet is inadequate is probably generally acceptable. The requirement that the fasting blood-sugar value should be maintained in the range of 110–130 mg./100 ml. (Pote *et al.*, 1958) means that there will be more early failures than if a critical value of 200 mg./100 ml. is used, as was done in the present investigation.

As in many earlier investigations, we also found that the treatment was more successful when (1) the onset of the disease was late in life (diet group), (2) the disease had been treated earlier by dietary regimen alone, (3) the disease had been of short duration before oral therapy was begun (insulin group), and (4) the insulin requirement had been small. The proportion of late failures was smaller in these groups, but it increased as the period of oral treatment lengthened. Since these groups generally comprise mild cases of diabetes, it would seem that oral diabetic treatment, even in mild cases, is merely able to postpone the use of insulin. But the milder the diabetes the longer this postponement will generally be.

In studying the possible causes of late failure we were able to ascribe the failure to dietetic negligence in one case only. Infection was not found to be more than temporarily an aggravating factor in any of the cases. Some of the late failures were due to the fact that our series was an unselected one and included some patients who were less suitable than others for oral treatment—for example, cases with an early onset. However, even among these there were cases still being successfully controlled after nearly three years of treatment. On the other hand, the occurrence of late failures in the groups which are generally regarded as well suited for oral therapy points to the probability that the drug, even in these cases—and possibly in all cases—gradually loses its effect during long-term administration. The failure of beta cells (Pfeiffer, 1957) can hardly be regarded as the cause of late failure of oral therapy, since the requirement of exogenous insulin did not increase after unsuccessful treatment. Also, after a short period of insulin treatment in late failures the reinstitution of oral therapy was sometimes successful. Further evidence supporting this conclusion is provided by animal experiments, in which very large doses of antidiabetic drugs (Bänder, 1957) given during nine months produced no changes in the pancreas histologically or in its insulin output.

Despite the fact that the benefit from oral treatment may be only temporary, this therapy is of considerable value in the treatment of mild diabetes. In the selection of patients for oral treatment the course which the disease has run in any particular patient does not always provide a good basis for estimating long-term results, since some of our successful cases had developed diabetes at an early age. A history of ketosis, which in the early days of oral therapy was regarded as a contraindication, does not always point to a late failure in the light of our results.

According to the present investigation the toxic effects of carbutamide were only slight. Since a number of reports (Bertram, 1958) provide evidence that it is more effective than, for example, tolbutamide in the treatment of diabetes consideration should be given to the use of carbutamide in suitable cases.

Summary

This investigation was carried out to assess the value of prolonged treatment with an orally administered antidiabetic drug, carbutamide. The series comprised 262 diabetics who had started on oral treatment 28 to 42 months earlier. The treatment was unsuccessful during the first month in 18% of a group of 148 patients with diabetes previously treated by diet alone. Later in the course of the treatment there were failures in 37% of the remaining cases in this group. Among these late failures were patients who were considered most suitable for this treatment—that is, those whose disease had developed in later life and was of short duration.

In the group of 114 patients previously treated with insulin there were primary failures during the first month in 56% and late failures in 50% of the patients who at first reacted successfully. The average insulin requirement did not increase after the failure of oral therapy.

No increase was observed in the complications of diabetes among those whose disease was successfully controlled by carbutamide. The untoward effects of the drug were slight even during long-term administration.

The occurrence of failures during long-term oral treatment, even among the patients apparently most suitable for this therapy, may point to a gradual disappearance of response to treatment, possibly due to some compensatory mechanism in the organism. In several cases of late failure of oral treatment, carbutamide regained its effectiveness, at least for a time, after the patient had been treated with insulin.

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PROLONGED CORTICOSTEROID THERAPY IN CHRONIC ASTHMA

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Though the value of corticosteroids in controlling acute episodes of bronchial asthma has been proved beyond reasonable doubt (Medical Research Council, 1956a; Walton, 1956; Thursby-Pelham and Kennedy, 1958), the place of these agents in the treatment of chronic asthma still remains an unsolved problem and, at times, a matter of fierce controversy (Herxheimer, 1955; Medical Research Council, 1956b; Brockbank *et al.*, 1957).

A corticosteroid preparation administered for 7 to 10 days to a patient with chronic asthma will often provide considerable or even complete relief of wheeze and dyspnoea, but the effect is temporary and symptoms recur with monotonous regularity at varying intervals after each course of treatment. Often in these cases a clinician, in desperation, resorts to continuous corticosteroid therapy on a long-term basis; in many instances he is persuaded to adopt this policy by patients who have already experienced the dramatic but tantalizingly short-lived relief afforded by brief courses of treatment. Such patients are exposed to the very real danger of the side-effects so commonly encountered with prolonged corticosteroid therapy. The clinician's dilemma is to decide whether the benefits of treatment outweigh the risks.

It is generally accepted that the danger of corticosteroid therapy is related both to the size of the daily dose and to the duration of treatment. In our experience it is seldom possible to suppress chronic asthma completely with a daily dose of less than 10–15 mg. of prednisolone. Within a few months, however, this level of dosage will produce minor, yet unpleasant side-effects, and in the course of a year or so render the patient liable to the major complications of corticosteroid therapy. In this paper we describe our efforts to provide a useful measure of symptomatic improvement with a minimum of side-effects by giving treatment intermittently instead of continuously, and so reducing the total intake of corticosteroid.

The investigation was planned so as to compare the results of intermittent treatment with prednisolone in a dosage equivalent to an average daily intake of less than 10 mg. with those of *continuous* treatment in a daily dose of 10–15 mg. Two groups of patients with chronic asthma were given intermittent treatment and a third group received continuous treatment. In the two groups having intermittent treatment the total dose of prednisolone was the same, but the rhythm of administration differed (see below). Treatment was given in two phases, during the second of which the dose of prednisolone was increased by 50% in both groups. In order to determine whether intermittent therapy was of genuine value in patients claiming a subjective improvement, inert tablets were at some stage substituted for prednisolone tablets.

The patients on continuous treatment received prednisolone twice or thrice daily for periods of up to three years. In some cases triamcinolone was administered for part of the time.

Selection of Cases and Allocation to Treatment Groups

All the 33 cases studied had chronic asthma. Their symptoms had been severe and virtually constant for at least two years, having failed to respond to treatment along generally accepted lines with bronchodilator drugs. Many patients had chronic bronchitis in addition to asthma. Those with a past history or present evidence of congestive cardiac failure were excluded.

At the time the investigation began we were not certain that intermittent treatment in severe cases was completely safe. We therefore did not feel justified in allocating patients at random to the three groups.

Twenty adult patients (7 male and 13 female) with chronic asthma of moderate severity were therefore given intermittent treatment, 10 in group A and 10 in group B. The patients in these two groups were matched as closely as possible with regard to age, sex, and severity of asthma. Group C consisted of 14 patients (8 male and 6 female), aged between 11 and 60 years, with more severe chronic asthma, who received continuous treatment with prednisolone or triamcinolone for periods of between one and three years. Seven of these patients had been treated in this way for several months before the investigation began: six had previously received intermittent treatment with cortisone or prednisolone outside the present investigation; the other patient was transferred from group B to group C because of his failure to respond to intermittent treatment. This transfer accounts for the total number of cases in the treatment groups (34) exceeding by one the total number of cases studied (33).

Procedure

All patients were given a preliminary course of either cortisone, 100 to 200 mg., or prednisolone, 20 to 40 mg., daily for at least seven days before long-term therapy was instituted. In general, cortisone was used for this purpose until 1957, but when prednisolone became available it was used almost exclusively. The object of the preliminary course of treatment was twofold: (*a*) to ensure that so far as possible all patients entered the long-term trial with approximately the same advantage so far as corticosteroid therapy was concerned: and (*b*) to determine whether the results of long-term treatment were related to the initial response to corticosteroids. No case was excluded from the long-term trial solely because of failure to respond to the initial course of corticosteroid therapy. The detailed procedure in the individual groups was thereafter as follows:

Intermittent Treatment (Groups A and B)

For the first six months of treatment (phase 1) the patients in both groups were given a total of 160 mg. of prednisolone during each four-week observation period in two different rhythms of dosage. Those in group A received 5 mg. four times daily on two

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consecutive days only per week, while those in group B were given the same daily dose for only the first eight consecutive days of each four-week period. These regimes were maintained for 20 weeks in 19 cases and for 16 weeks in one.

A clinical assessment, along with an estimate of forced expiratory volume (F.E.V.), was made at four-weekly intervals in every case. The assessments were invariably carried out on the day before the resumption of treatment—that is, when patients in group A had received no treatment for five days, and those in group B none for 20 days.

During the second phase of treatment the total dosage of prednisolone given during each four-week period was increased by 50%, from 160 to 240 mg., the principle of intermittent administration being maintained. This was done by changing the number of days on treatment from two to three consecutive days each week in group A and from eight consecutive days every four weeks to six consecutive days a fortnight in group B, the dose of prednisolone being maintained at 5 mg. four times daily. Twelve of the 20 patients in phase 1 entered phase 2 of treatment, five from group A and seven from group B. Of the eight patients who did not proceed to phase 2, four were withdrawn from the trial because they lived many miles from the hospital and were unable to attend regularly, and two because they had become so introspective that it was thought desirable to curtail the frequency of their visits. In the seventh patient corticosteroid treatment was withdrawn because of excessive gain of weight, and the eighth had to be transferred to group C for treatment with daily prednisolone.

Phase 2 continued for at least 12 weeks, the clinical assessments and estimates of F.E.V. being carried out at four-weekly intervals as in phase 1.

Continuous Treatment (Group C)

Patients in this group were treated continuously with prednisolone for periods of 15 months to over three years. The dose prescribed was 5 mg. thrice daily for adults and 5 mg. twice daily for children under the age of 14 years. In 9 of the 14 cases triamcinolone, in a dose of 6 to 12 mg. daily, was later substituted for prednisolone because of claims made that it caused fewer side-effects. No attempt was made at a comparative assessment of the two corticosteroids.

Clinical assessments and estimations of F.E.V. were carried out at four-weekly intervals as in groups A and B.

Other Treatment

Treatment other than with corticosteroids was at the discretion of the clinician in charge of the patient. Bronchodilator agents were seldom used, apart from inhalations of adrenaline and isoprenaline aerosols to control excessive bronchospasm, but antibiotics were often required for respiratory infection, the form of treatment usually favoured being tetracycline, 0.25 g. four times daily for five to seven days.

In an attempt to prevent permanent depression of adrenal function, all patients on continuous corticosteroid therapy received corticotrophin, 30 units on two consecutive days fortnightly or monthly. After we had encountered osteoporosis and spontaneous fracture in one patient in 1957, all adult males receiving corticosteroids daily were given sublingual testosterone, 25 mg. on alternate days. Adult females received a non-virilizing androgen, methylandrostanolone. None of the patients on intermittent corticosteroid therapy received corticotrophin or androgens.

Assessment of Progress

Clinical Observations.—The response to treatment was defined as follows: (1) Satisfactory: the patient was relieved of serious asthmatic symptoms for 75% of each four-week period and was able to resume a mode of life previously made impossible by chronic asthma. (2) Fair: definite though less impressive relief was obtained for approximately 30 to 70% of each four-week period. (3) Unsatisfactory: the relief obtained was no better than could be expected from ordinary measures.

Serial Estimations of F.E.V.—The method employed was that described by Needham *et al.* (1954) with a time interval of two seconds. A shorter time interval could not be used as the apparatus required for this was not available until the trial had been in progress for some months. At the beginning of the investigation the maximum voluntary ventilation (M.V.V.) was also measured, but this was later abandoned, as the rapid breathing required to make the test accurate tended to produce wheezing or to increase its degree, thus making the test unreliable from the observer's point of view and unpopular with the patients. To a less extent the performance of three or four estimations of F.E.V. in rapid succession also caused a slight increase in wheezing, and it was frequently observed that the first recording obtained was the highest. The highest value was always accepted. The values of F.E.V. obtained have been expressed as a percentage of the predicted normal value for each patient (Needham *et al.*, 1954).

Results of Intermittent Treatment (Groups A and B)

The results of the four-weekly clinical assessments were similar in the two groups. In phase 1 a satisfactory clinical response was recorded in 23 (46%) and a fair response in 20 (40%) of the 50 clinical assessments made in the patients in group A. In group B a satisfactory clinical response was recorded in 22 (45%) and a fair response in 18 (37%) of 49 similar clinical assessments. At the time of each assessment the patients were asked whether the asthma was any better on the days on which prednisolone was taken. Five of the 10 patients in group A and 8 of the 10 in group B said that such an association existed. This difference between the results in the two groups is not unexpected, in view of the longer consecutive period of treatment in group B. In general, the patients who did not experience an improvement on the days they were taking prednisolone tablets were those who showed the poorest results at four-weekly assessments.

The results of serial estimations of F.E.V. obtained before treatment, after the preliminary intensive course of prednisolone, and for the following 16 to 20 weeks, are shown in the form of a scattergram in the first sections of Figs. 1 and 2. The results were similar in the two groups, and in both the mean value of F.E.V. was always above the pre-treatment level. In the last four to eight weeks, however, the mean F.E.V. was well below the optimum level recorded after seven days' intensive treatment, and in some cases the improvement in function in the later stages was negligible. It must be remembered, however, that all the estimations of F.E.V. were made at a time when the patient was least

likely to be obtaining benefit from prednisolone. No attempt was made to obtain recordings of F.E.V. during the periods when the patients were taking prednisolone tablets.

During phase 2 the patients in group A recorded a satisfactory response on 50% of the clinical assessments as compared with 46% in phase 1, while those in group B recorded a satisfactory response on 73% as compared with 45% in phase 1. These results seemed to suggest that there was slightly greater improvement with the change to treatment on six consecutive days per fortnight (group B) than with that to three consecutive days per week (group A), but estimations of F.E.V. (Figs. 1 and 2) did not provide objective confirmation of the superiority of this treatment regime.

Prednisolone therapy was interrupted in 18 of the 20 cases in groups A and B, by substituting inert tablets without the patient's knowledge, the clinician observing progress or the respiratory physiologist estimating F.E.V. Psychological or geographical reasons rendered such a change inadvisable in the remaining two cases. The substitution was never made before the 16th week of phase 1 of treatment, and in some cases it was deferred until phase 2 was in progress. Within four weeks of the interruption of treatment the clinician reported marked deterioration in nine patients, moderate deterioration in three, and slight deterioration in four. In two patients the change was not detected by the clinician. In several cases the deterioration was so striking that the patient was referred to the hospital as an emergency case by the general practitioner. When a deterioration was recorded by

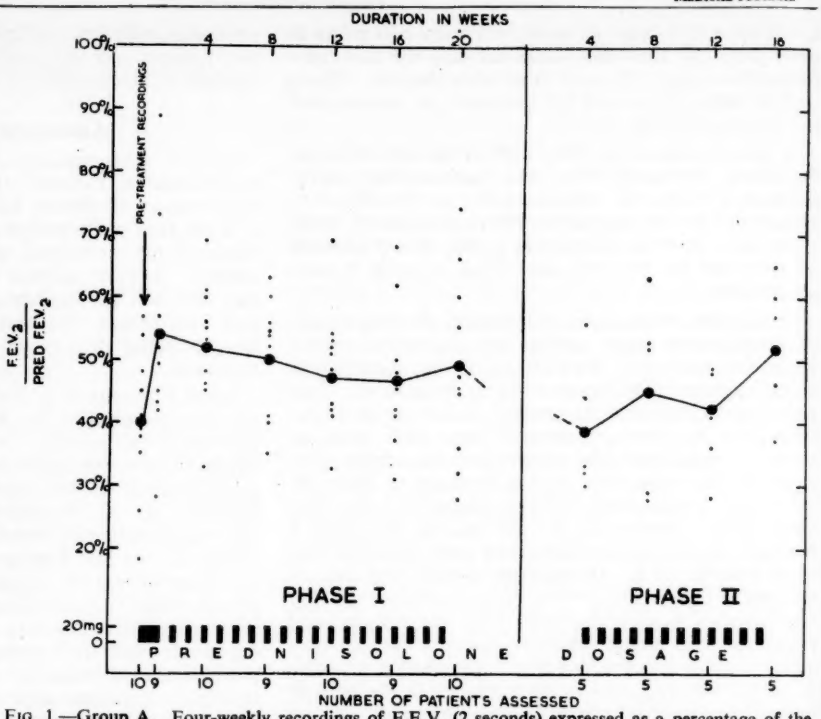

FIG. 1.—Group A. Four-weekly recordings of F.E.V. (2 seconds) expressed as a percentage of the predicted normal value in 10 patients treated with prednisolone, 20 mg. a day. Phase I—on two consecutive days a week. Phase II—on three consecutive days a week. (Mean level represented by unbroken line.)

In Figs. 1, 2, and 3 the number of recorded points at each four-weekly assessment does not always add up to the total number of patients under observation. Such omissions usually occurred because the patient did not feel well enough to perform the tests or because he or she could not attend at the proper time. The absence of these recordings may cause the average figures to appear more favourable than would have been the case had all the patients been tested on all occasions.

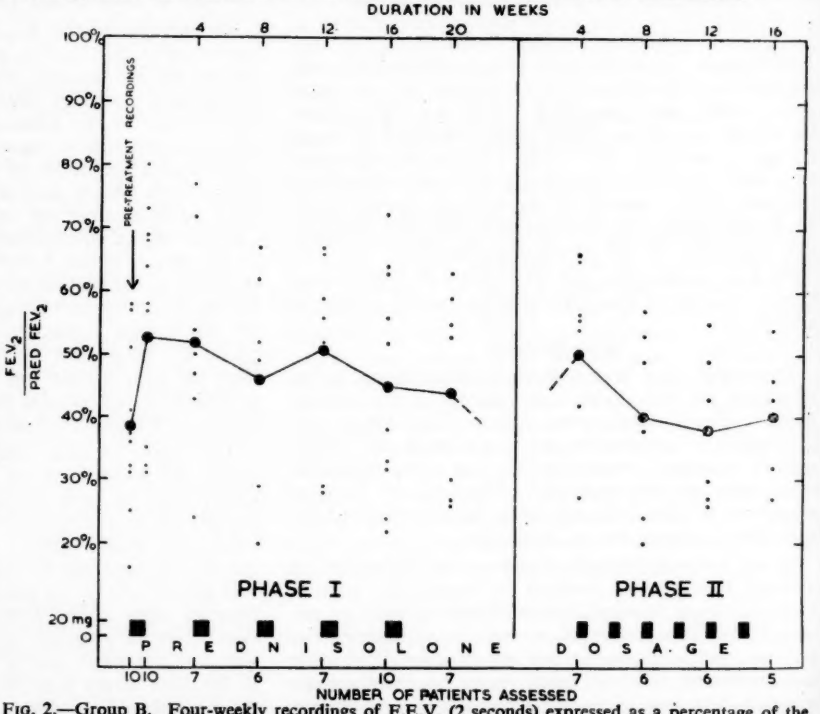

FIG. 2.—Group B. Four-weekly recordings of F.E.V. (2 seconds) expressed as a percentage of the predicted normal value in 10 patients treated with prednisolone, 20 mg. a day. Phase I—on eight consecutive days every four weeks. Phase II—on six consecutive days every two weeks. (Mean level represented by unbroken line.)

the clinician he was informed of the change of treatment and prednisolone therapy was resumed. In all such cases the asthmatic symptoms returned to their former level within four to eight weeks.

The effect on F.E.V. of interrupting intermittent prednisolone therapy is shown in Table I. The figures in the first column indicate the level of the F.E.V. for each patient on the day before the change to inert tablets was made, and the subsequent changes in F.E.V. are shown in the second column. The fact that an unbiased observer was able to recognize a deterioration in no fewer than 16 of the 18 patients in whom treatment was interrupted, and that this deterioration was reflected in a marked reduction in F.E.V., leaves little doubt about the existence of a causal relationship between the interruption of treatment and the increase in asthmatic symptoms.

TABLE I.—*Effect on F.E.V. (Expressed as Percentage of Predicted Normal) of Substituting Inert Tablets for Prednisolone in Patients Treated in Groups A and B*

F.E.V. before Substitution of Inert Tablets (% of Predicted Normal)	F.E.V. after Substitution of Inert Tablets (% of Predicted Normal)	Interval between F.E.V. Estimations (Days)
	Group A	
52	42	28
53	22	28
36	31	28
*26	18	28
29	25	28
63	57	28
69	48	28
40	Too ill to attend	8
41	18	7
	Group B	
49	44	28
26	34	28
*43	36	28
33	Unfit for tests	28
53	31	28
52	43	20
69	33	17
42	15	14
66	40	7

* In these two patients a clinical deterioration was not recognized by the observer.

Results of Continuous Treatment (Group C)

In 8 of the 14 cases there was a dramatic clinical improvement, which was maintained throughout the whole period of treatment. These patients all eventually became asymptomatic and their way of life changed from one of chronic invalidism to almost complete normality. In three, the improvement was considerable but not constant. In the other three there was apparently no response to treatment, and corticosteroid therapy was discontinued a few months later. Over a period of two years 206 four-weekly clinical assessments were made of the 11 patients responding to treatment. A satisfactory response was recorded 172 times (83%), a fair response 24 times (12%), and an unsatisfactory response 10 times (5%). Two patients have been on continuous treatment for over three years and four for over two years; in all six the good initial response to corticosteroids has been consistently maintained.

The results of serial estimations of F.E.V. over the first two years are shown in Table II and Fig. 3. The three patients who showed no improvement are omitted from Table II and are specifically identified in Fig. 3, in which it is evident that their F.E.V. showed no increase above the pre-treatment level throughout. All the others showed a striking improvement, the average F.E.V. for every four-week period being twice that of the pre-treatment figure. Triamcinolone appeared as satisfactory as prednisolone in the treatment of these cases.

Relationship of Initial Response to Corticosteroids and the Results of Long-term Treatment

The results are summarized in Table III. In the patients receiving continuous treatment there was a close relationship between the response of F.E.V. to the initial high-dosage treatment with corticosteroids and the subsequent response to long-term treatment with prednisolone or triamcinolone. For example, in the 11 patients in group C whose F.E.V. increased by more than 25% initially, this level of improvement was maintained in 71% of the subsequent F.E.V. recordings.

TABLE III.—*Results of Long-term Treatment Analysed According to Initial Response to Steroid Therapy*

*Increase in F.E.V.₁ following Initial Course of Steroid Therapy	No. of Patients	Response to Long-term Steroid Treatment. Increase in F.E.V. at Four-weekly Intervals			Total No. of F.E.V. Recordings
		<10%	10–25%	>25%	
Groups A and B:					
Less than 10%	8	17 (48%)	13 (37%)	5 (15%)	35
10–25% ..	4	5 (30%)	12 (70%)	0	17
Over 25% ..	8	16 (48%)	7 (22%)	10 (30%)	33
Group C:					
Less than 10%	0	0	0	0	0
10–25% ..	3	21 (95%)	1 (5%)	0	22
Over 25% ..	11	15 (8%)	43 (21%)	148 (71%)	206

* The increase in F.E.V. is expressed as a percentage of the predicted normal value for each patient. Patients in groups A and B received prednisolone intermittently and those in group C received prednisolone or triamcinolone continuously.

On the other hand, there was no such relationship in the patients in group A and B receiving prednisolone intermittently. In the eight patients whose F.E.V. increased by more than 25% initially, this increase was maintained in only 30% of subsequent recordings. Neither with continuous nor with intermittent treatment was a satisfactory long-term result obtained when the initial response was poor.

TABLE II.—*Analysis of the Recordings of F.E.V. (2 seconds), Expressed as a Percentage of the Predicted Normal Value in the 11 Patients Successfully Treated with Continuous Prednisolone (P.) or Triamcinolone (T.)*

Case No.	Age	Duration Continuous Treatment (Months)	Values of F.E.V.				Type of Treatment		
			Pre-treatment	At 1 Month	At 1 Year	At 2 Years	At 1 Month	At 1 Year	At 2 Years
1	13	15 (4P. 11T.)	34	73	46	100 (15th month)	P.10	T.6	T. 6
2	14	21 (14P. 7T.)	43	81	84	81 (21st ,,)	P.10	P.10	T. 6
3	47	21 (17P. 4T.)	23	57	97	74 (,, ,,)	P.15	P.10	T. 8
4	56	36 (All P.)	29	67	63	63	P.15	P.15	P.10
5	15	27 (23P. 4T.)	16	49	27	60	P.15	P.10	T. 8
6	14	29 (24P. 5T.)	44	58	56	63	P.15	P.10	T. 8
7	17	24 (All P.)	21	60	44	49	P.15	P.15	P. 7·5
8	10	42 (37P. 5T.)	26	84	83	54	P.10	P.10	P.10
9	21	40 (35P. 5T.)	47	81	85	68	P.15	P.15	P.10
10	58	26 (22P. 4T.)	23	93	81	78	P.15	P.15	T. 8
11	63	24 (19P. 5T.)	32	65	58	66 (22nd month)	P.15	P.15	T. 8

The numerals in the treatment column indicate amount of drug in milligrams administered daily. Only 7 patients are shown as having changed from prednisolone to triamcinolone. Cases 8 and 9 did so after the second year of treatment.

Side-effects from the Administration of Corticosteroids

Minor Side-effects.—The two side-effects most commonly encountered with prednisolone were "moon-face" and excessive weight gain. These occurred in almost all the patients who received prednisolone daily but not in any of those given intermittent therapy. The gain in weight was readily controlled by attention to diet, provided the patient co-operated. It appears that moon-face cannot be avoided if a relatively high dosage of prednisolone is given. With the change to triamcinolone, moon-face was commonly unaltered, but five out of nine patients showed slight loss of the weight gained during the period of treatment with prednisolone.

Serious Side-effects

Four patients, all of whom were receiving prednisolone daily (group C), developed one of the serious side-effects of corticosteroid therapy, and in one of these patients two such complications were encountered.

Osteoporosis and Fracture.—A spontaneous fracture of the shaft of the left femur occurred in Case 4 (Table II) after daily treatment with corticosteroids for two and a half years and is reported in detail elsewhere (Lamb and Somner, 1958). In Case 10 a compression fracture of a lumbar vertebra developed after prednisolone daily for 10 months. This fracture was associated with a fall, but prednisolone probably contributed to the ease with which it occurred.

Tuberculosis.—A girl of 10 years (Case 8) developed an active tuberculous lesion in the lung after daily treatment with prednisolone for 14 months, but this responded completely to antituberculous drugs while prednisolone therapy was maintained.

Peptic Ulcer.—A woman aged 54, who had received prednisolone daily for five months without a satisfactory response, developed abdominal pain and was shown on radiological examination to have an ulcer crater in the duodenum. Patient No. 4, who had previously sustained a spontaneous fracture while on corticosteroid therapy, developed dyspeptic symptoms 11 months later and was found on radiological examination to have two ulcer craters in the duodenum. In the interval between healing of the fracture and the development of dyspepsia 10 mg. of prednisolone was given daily.

Evidence of severe adrenal depression with failure to respond to corticotrophin stimulation has been found in all but 2 of the 11 patients who received prednisolone or triamcinolone continuously for more than one year. The results of these investigations will be reported later.

No serious side-effects were encountered in any of the 20 patients receiving intermittent corticosteroid therapy in groups A and B.

Factors Concerned in the Response to Long-term Corticosteroid Therapy

Those patients with chronic asthma who did not respond to corticosteroid therapy all had a greater degree of associated chronic bronchitis than those who did; in addition, many of them were subject to frequent episodes of respiratory infection. In those cases the appearance of pus in the sputum often heralded a return of asthma, which previously had been well controlled by either continuous or intermittent corticosteroid

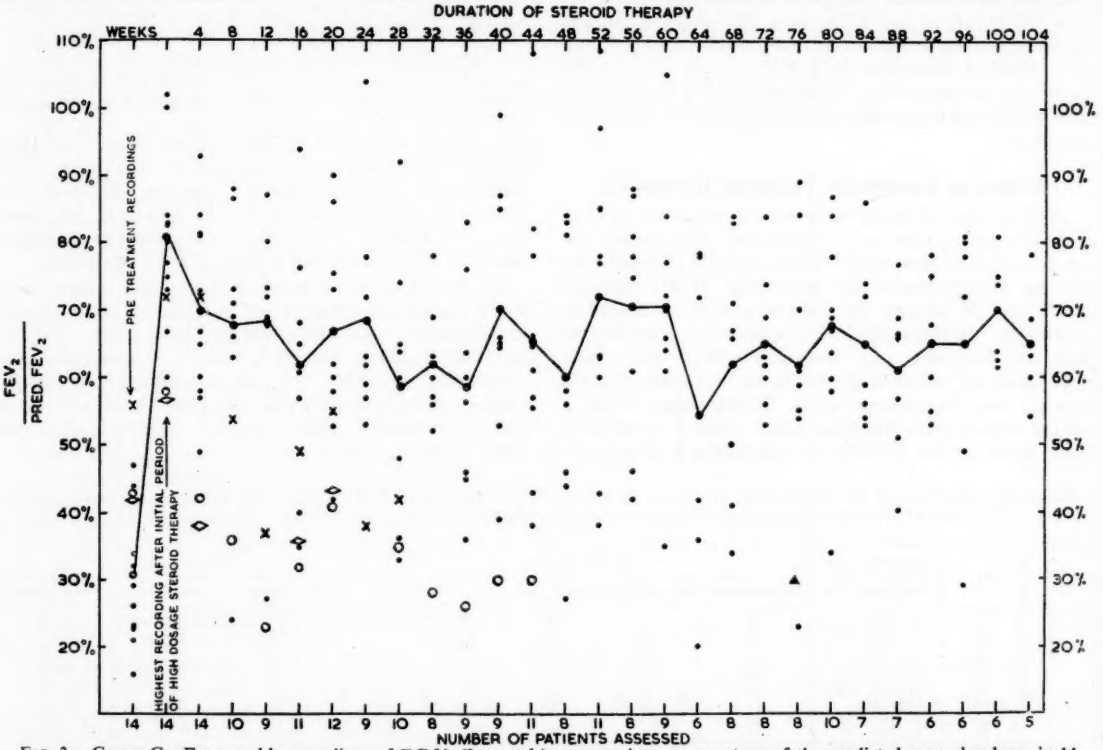
DURATION OF STEROID THERAPY
WEEKS
4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104
110%
100%
90%
80%
70%
60%
50%
40%
30%
20%
PRE TREATMENT RECORDINGS
HIGHEST RECORDING AFTER INITIAL PERIOD OF HIGH DOSAGE STEROID THERAPY
FEV2 / PRED. FEV2
14 14 14 10 9 11 12 9 10 8 9 9 11 8 11 8 9 6 8 8 8 10 7 7 6 6 6 5
NUMBER OF PATIENTS ASSESSED

FIG. 3.—Group C. Four-weekly recordings of F.E.V. (2 seconds) expressed as a percentage of the predicted normal volume in 14 patients receiving continuous treatment with prednisolone or triamcinolone. (Mean level represented by unbroken line.) ✧, ○, × =Identity recordings of the three patients who showed no response to initial course of prednisolone and whose subsequent response remained unsatisfactory. All have been excluded from calculation of means.

therapy. The frequency of respiratory infection and its liability to precipitate asthma was much greater in those receiving intermittent therapy than in those being treated continuously. There are two possible reasons for this. The first is that in the allocation of cases to intermittent or continuous corticosteroid therapy a higher proportion of patients who were particularly subject to respiratory infection were included in the group receiving intermittent therapy. The second and more likely explanation is that the relative freedom from asthma experienced by patients given continuous therapy ensured more efficient bronchial drainage and rendered them less liable to develop respiratory infection.

The reason why the patients on intermittent treatment (groups A and B) who had exhibited a good response to the preliminary intensive course of corticosteroid therapy obtained less benefit from long-term treatment than those treated continuously (group C) probably was that the patients in groups A and B were denied the opportunity of maintaining their good initial response because of the restricted dosage of prednisolone.

Conclusions

It can be stated with confidence on the basis of this investigation that continuous treatment with prednisolone, 10–15 mg. daily, or triamcinolone, 6–12 mg. daily, as given to the 14 patients in group C of this series, will, in a majority of cases, suppress the symptoms of chronic asthma for long periods. Such a result can be expected when chronic bronchitis and recurrent respiratory infection are not conspicuous features and when an obvious clinical improvement accompanied by an abrupt increase in F.E.V. rapidly follows the start of treatment. Eight patients satisfying these criteria have achieved a remarkable measure of sustained symptomatic improvement. There has been nothing to suggest that the treatment becomes any less effective with the passage of time, even in patients who have received prednisolone continuously for two or three years. Chronic bronchitis and recurrent respiratory infection were the factors probably responsible for the failure of the other six patients to obtain a sustained response.

Unfortunately these results are offset by the frequency of serious side-effects which occurred in 4 of the 14 patients treated continuously. Progress is, however, being made in the management of two of the more important side-effects—tuberculosis and osteoporosis. Periodical chest radiographs will detect the development of pulmonary tuberculosis, which, if active, can be effectively controlled by antituberculous drugs without interrupting the corticosteroid therapy. Osteoporosis due to the katabolic effect of corticosteroids on the protein matrix of bone may be inhibited and osteoblastic bone formation encouraged by the administration of testosterone and other anabolic steroids. Unfortunately, it is usually impossible to discover the presence of a peptic ulcer until the appearance of dyspepsia. Furthermore, it is unwise to continue oral corticosteroid treatment in such cases because of the danger of haematemesis or perforation.

There are undoubtedly some patients with chronic asthma in whom respiratory distress is so crippling that even if serious side-effects were inevitable it might still be preferable to accept the consequences rather than to deny such patients the prospect of relief which corticosteroid therapy alone can offer.

It was this therapeutic impasse which prompted the present investigation into the value of regimes of corticosteroid therapy employing dosages apparently below the danger level. The small numbers in the various treatment groups have made assessment difficult and possibly unreliable, but we feel justified in drawing the following tentative conclusions:

1. Prednisolone in a dose of 10–15 mg. a day, or triamcinolone 6–12 mg. daily, is capable of suppressing chronic asthma indefinitely in a high proportion of cases, but at this level of dosage minor side-effects are common and serious side-effects by no means rare.

2. Prednisolone given intermittently in a dose of 20 mg. a day on either two or three consecutive days of every week, on eight consecutive days of every month, or on six consecutive days of every fortnight provides a useful though fluctuating degree of symptomatic improvement for an indefinite period apparently without any serious danger from side-effects.

3. The response to long-term prednisolone therapy, whether given continuously or intermittently, is adversely influenced by chronic bronchitis and by frequent episodes of respiratory infection. Patients in whom a marked improvement is not rapidly obtained after they have been given prednisolone in a dose of 20 mg. a day seldom benefit from long-term treatment, whether continuous or intermittent.

Summary

An attempt has been made to assess the value of long-term corticosteroid therapy in relieving symptoms of chronic asthma in 33 patients. The assessments, at four-weekly intervals, were made clinically and by estimation of forced expiratory volume.

Ten patients were given prednisolone on either two or three consecutive days of each week and another 10 either on eight consecutive days per month or on six consecutive days each fortnight. These various regimes provided a useful but fluctuating degree of symptomatic improvement.

A group of 14 patients received prednisolone or triamcinolone daily for periods varying from 15 months to over 3 years. A remarkable measure of sustained improvement was obtained in eight. The presence of chronic bronchitis in addition to chronic asthma was believed to be the main reason why the other six patients failed to show an equally satisfactory response.

Serious side-effects from corticosteroid drugs were encountered in four patients given continuous treatment. Such treatment can be recommended only in exceptional cases where there is no effective alternative.

We thank Professor John Crofton for his co-operation and help in the preparation of this paper, Nurse E. Hulbert for her care of the patients at the clinic, and Mrs. Joan Valentine and Miss Winifred Tait for much secretarial assistance. We are grateful to Miss Sylvia Merchant for undertaking many of the respiratory-function tests.

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NASAL STAPHYLOCOCCI AND SEPSIS IN NEWBORN BABIES

BY

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In a previous study in this hospital an attempt was made to trace the pathways by which staphylococci spread in a nursery (Cook *et al.*, 1958). The method used was based on the finding that, in the absence of special measures, all the newborn babies carried *Staphylococcus aureus* in the nose by the twelfth day of life. Certain measures, and in particular the application of triple dye to the umbilical stump, reduced the nasal colonization rate. This work has been continued. Air disinfection with ultra-violet light and bathing with hexachlorophane have been assessed as a means of preventing nasal carriage. Williams *et al.* (1959) have shown that adult patients in this hospital who are nasal carriers are more likely to suffer staphylococcal sepsis than those who are not carriers. We have found a similar relationship between sepsis and the carriage state in newborn babies. If this is a general finding it provides a practical reason for attempting to prevent the colonization of newborn babies by *Staph. aureus*.

Methods

Babies.—The babies were full-term and breast-fed. Where breast-feeding did not become established, the babies were nevertheless taken to the mothers for either a breast-feed with complement or a bottle-feed. Babies and mothers normally went home on the 12th day.

Nurseries and Staff.—These were as described by Cook *et al.* (1958). Masks and gowns were not worn.

Bacteriology.—Noses were examined daily, except on Sundays, by rubbing dry cotton-wool swabs six times round the inside of each nostril. Staphylococci which coagulated plasma were regarded as *Staph. aureus*.

Results

Carriage of Staph. aureus

Throughout the trial, triple dye* was applied at birth and thereafter daily to the umbilical stumps of all the babies in each group.

Babies Treated with Triple Dye Only.—One hundred and ten babies were treated with triple dye to the umbilical stump, without any other special measure. Of these, 38 (35%) were still not carriers of *Staph. aureus* by the 12th day of life (Table I). In the previous trial of this method 17 out of 55 babies (31%) were found not to be nasal carriers by the 12th day.

Effect of Air Disinfection with Ultra-violet Light.—As it is possible that staphylococci reach babies through the air, the effect of air disinfection with ultra-violet light was tested. The apparatus used was designed to circulate 1,000 cu. ft. (28.3 cu. m.) of air a minute past four ultra-violet-light tubes. This rate meant that in the large nursery the air was passed through the disinfector approximately seven times an hour, and more often in the small nursery. The 30-watt low-pressure mercury tubes, each 3 ft. (90 cm.) long, had an ultra-violet output of approximately 6 watts at 2537Å. They were placed parallel to the direction of air-flow at the corners of a square of side 12 in. (30 cm.) set symmetrically in a 3 ft. 6 in. (107 cm.) length of square section duct approximately 23½ by 23½ in. (60 by 60 cm.) inside dimensions. The average number of staphylococci in the nursery air was reduced, especially during periods of activity, when the disinfector was in use (Table II), but, despite reduction in the air counts, we could find no appreciable differences in the nasal colonization rates. Of 97 babies, 35 (36%) were still negative on the 12th day (Table I).

Effect of Washing the Babies with Hexachlorophane.—Hexachlorophane, after the first few babies, was used as "phisohex," a proprietary preparation containing amongst its ingredients a detergent and 3% hexachlorophane. Babies were bathed daily. A lather was produced with phisohex, which was then rinsed off in the bath. There was some indication of a reduction in the air counts of staphylococci during the period of hexachlorophane treatment, though this reduction was less than that seen when air was disinfected by ultra-violet light. Nevertheless triple dye and hexachlorophane were more successful than triple dye alone or triple dye and ultra-violet light in preventing nasal colonization. There were 105 babies in this group, and 48 (46%) of them were still negative on the 12th day.

*Triple dye=brilliant green, proflavine hemisulphate, and crystal violet.

TABLE I.—*Nasal Carriage of Staph. aureus by Newborn Babies. Babies Becoming Carriers on Successive Days of Life*

Day of Life	Triple Dye	Triple Dye and Ultra-violet Light	Triple Dye and Hexachlorophane
1	1	2	1
2	3	2	3
3	11	6	8
4	9	18	10
5	9	10	13
6	10	8	8
7	6	5	2
8	6	7	4
9	4	4	5
10	5	0	2
11	4	0	1
12	4	0	0
Negative on 12th day	38 (35%)	35 (36%)	48 (46%)
Total ..	110	97	105

TABLE II.—*Bacterial Air Counts in Babies' Nurseries in Varying Circumstances*

Nursery		Treatment	Quiet			Activity		
			No. of Samples	Mean Counts/cu. ft.		No. of Samples	Mean Counts/cu. ft.	
				Staph. aureus	General		*Staph. aureus*	General
Small		Triple dye ..	52	0·031	9·9	23	0·091	26·6
		T.D.+ ultra-violet	64	0·020	5·8	18	0·038	20·5
Large		T.D. ..	35	0 031	5·9	11	0·106	15·4
	(1)	T.D.+air circulation	35	0·020	7·2	8	0·140	12·1
		T.D.+ ultra-violet	82	0·014	7·1	22	0·026	9·2
	(2)	T.D.+ hexachloro-phane ..	177	0·026	8·5	31	0·059	13·7

(1) Triple dye with air circulation by the disinfector, but ultra-violet not on.
(2) Hexachlorophane, either as soap ("cidal") or "phisohex."

Sepsis

A record was made of sepsis as it occurred in the 312 babies involved in this study. The figures presented here are only for sepsis due to *Staph. aureus*, or, in

cases where no swab was taken, for sepsis thought on clinical grounds to be due to staphylococci.

In all, 24 babies (7.7%) suffered staphylococcal sepsis. In 12 of these the diagnosis was made by isolation of the staphylococcus; in 12 the diagnosis was presumptive. Sepsis was distributed almost equally between the three groups of babies—7 cases among the 110 babies treated with triple dye only, 11 cases among the 97 babies treated with triple dye in conjunction with air disinfection, and 6 cases in the 105 babies treated with triple dye and hexachlorophane.

Sepsis in Relation to Nasal Carriage of Staph. aureus.—It has been shown that adult patients in this hospital are more likely to develop staphylococcal sepsis if they are nasal carriers of *Staph. aureus* than if they are not (Williams *et al.*, 1959). It was therefore of interest to see if the same trend was present in the babies. Of the 312 babies, 191 carried staphylococci by the 12th day. In this group there were 20 babies (10.5%) with staphylococcal sepsis during their stay in hospital. The remaining 121 babies were not found to be carriers by the 12th day of their life in hospital. Of these, only 4 (3.3%) developed staphylococcal sepsis. In 16 babies who were carriers and developed sepsis, staphylococci were isolated from the nose before the onset of sepsis. In a further two babies the isolation was made from the nose and septic lesion at the same time.

Discussion

In our previous work in these nurseries we found two measures that appreciably affected the nasal colonization rate of newborn babies. These were the application of triple dye to the umbilical stump, and the use of individual gowns for each baby. Combination of these two methods was no more successful than either method alone. This should be borne in mind when assessing the present results. The failure of air disinfection by ultra-violet light to alter the nasal rate despite an undoubted effect on the number of bacteria in the air clearly shows that a reduction in the number of bacteria in the environment is not necessarily followed by a reduced rate of staphylococcal spread. If, however, the ultra-violet light had been used uncombined with triple dye, a result due to it alone might have been seen. The failure may have been observed because the aerial transfer of staphylococci was not important in the circumstances, though other explanations are possible.

Hexachlorophane is used in many North American nurseries. Baldwin *et al.* (1957), for instance, found that it reduced the rate of infants' nasal colonization below that reported in other investigations. Our results support these findings in that, though the difference was not statistically significant, the nasal colonization rate was lowest with hexachlorophane bathing in conjunction with triple dye to the umbilical stump.

But there is still a long way to go. Even with our best regimen more than half the babies became nasal carriers before leaving hospital. That this phenomenon was of clinical and not only academic importance was strongly suggested by the analysis of sepsis. Staphylococcal sepsis occurred three times as often in babies who became carriers of *Staph. aureus* as it did in those who remained negative, and in most cases carriage preceded sepsis. This ratio is very close to that reported for adults. If it means, as it apparently does, that carriage of staphylococci conduces to sepsis, it provides a further incentive and justification for attempts to prevent the colonization of newborn babies by *Staph. aureus.*

Summary

An attempt has been made in a hospital nursery to prevent the colonization of newborn babies' noses by *Staph. aureus.* When triple dye was applied to the umbilical stump 35% of babies were still not carriers by the 12th day of life. Air disinfection of the nursery with ultra-violet light combined with triple dye produced almost identical results. With triple dye and hexachlorophane 46% of babies reached the 12th day free from nasal staphylococci.

Staphylococcal sepsis occurred three times as often in babies found to be carriers as in those who were not.

We thank Dr. C. F. Harris for permission to conduct these trials and the Medical Research Council for a grant-in-aid. We are also much indebted to the sister in charge of the maternity ward and her staff for their co-operation, and to Miss O. Duke for technical assistance. Hexachlorophane was kindly supplied as phisohex by Bayer Products Ltd.

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MEGALOBLASTIC ANAEMIA DUE TO PHENOBARBITONE

THE CONVULSANT ACTION OF THERAPEUTIC DOSES OF FOLIC ACID

BY

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Megaloblastic anaemia may develop in patients treated with the anticonvulsant drugs phenytoin sodium and primidone (Badenoch, 1954; Hawkins and Meynell, 1954; Fuld and Moorhouse, 1956) and in patients receiving large doses of barbiturates (Hobson, Selwyn, and Mollin, 1956; Calvert, Hurworth, and MacBean, 1958). Though Hawkins and Meynell (1958) observed mild macrocytosis in about a third of the patients receiving phenobarbitone, megaloblastic anaemia due to this very widely used barbiturate has not been recorded.

The purpose of this paper is to describe a patient who presented with a megaloblastic anaemia on two occasions while taking large doses of phenobarbitone, and to report observations on the pathogenesis of the anaemia and the unusual response to treatment with folic acid.

Case Report

The patient, a known epileptic aged 43, was first seen in 1955 with rheumatoid arthritis. He was uncooperative, refused to attend for treatment, and developed permanent contractures of both knees and the left arm.

Since the age of 16 he had had grand-mal attacks, which were well controlled by 1.5 gr. (96 mg.) of phenobarbitone daily, and he had been free of attacks from 1954 up to the time of his admission to hospital in 1958. However, an electroencephalogram (E.E.G.) in 1955 (Fig. 1A) showed

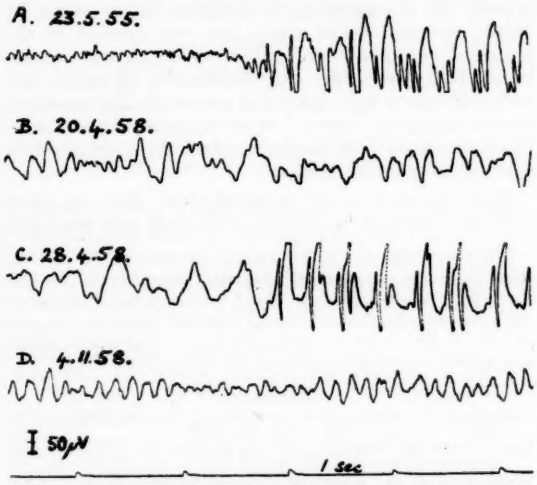

FIG. 1.—Electroencephalograms. A, Normal background activity followed by paroxysm typical of epilepsy. B, Severe generalized abnormality while taking large doses of phenobarbitone. C, Severe generalized abnormality leading to paroxysmal activity after treatment with large doses of folic acid. D, Background activity shows only mild generalized abnormality after withdrawal of both phenobarbitone and folic acid.

one short paroxysm consisting of regular, high-amplitude, bilaterally synchronous polyspikes and slow waves. The background activity was normal. The record was diagnostic of epilepsy.

After leaving hospital in 1955 he began to control his own dose of phenobarbitone, taking from 3 to 6 gr. (195 to 390 mg.) daily, most of the dose being taken at night.

For the previous year he had been bedridden owing to the contractures and was cared for by his mother. His diet during that year was said to have consisted of bread-and-butter, tea with milk, occasionally supplemented by a little meat or fish.

During the six weeks before admission he complained of anorexia, lassitude, and intermittent vomiting, and became increasingly pale. He was admitted to Hammersmith Hospital under the care of Dr. M. D. Milne in March, 1958.

On examination he was sallow, with gross pallor of the mucous membranes. No purpura or haemorrhages were present, and the gums were normal. There was bilateral ankle oedema. He was confused, uncooperative, and of low intelligence. Blood-pressure was 180/80, and a fourth heart sound was audible at the cardiac apex. Both the liver and spleen were palpable 2 cm. below the costal margin. There were marked muscle-wasting and flexion contracture of the left arm, and the lower limbs were fixed in extension at the knees. Ankle-jerks could not be elicited, plantar responses were flexor, and there was a variable sensory loss in the lower limbs.

Investigations

A blood count showed red cells, 1,200,000/c.mm.; Hb, 5.5 g./100 ml.; P.C.V., 17%; reticulocytes, 0.1%; M.C.V., 141 cubic microns; M.C.H.C., 32%; leucocytes, 4,200/c.mm. (neutrophils 74%, lymphocytes 16%, monocytes 6%, eosinophils 4%); platelets, 125,000/c.mm. The stained film showed macrocytosis, poikilocytosis, anisocytosis, hypersegmentation of the neutrophils, and occasional myelocytes. Aspiration of sternal marrow revealed severe megaloblastic haemopoiesis. The serum vitamin-B_{12} level measured by microbiological assay with *Euglena gracilis* (Ross, 1952) was within the normal range, being 230 $\mu\mu$g./ml.

A fractional test meal showed the presence of free acid in the gastric juice; the absorption of radioactive vitamin B_{12} measured by the hepatic uptake method of Glass (1954) was within normal range, an estimated 0.4 μg. being absorbed from a 1-μg. dose of ^{58}Co–vitamin B_{12}. Fat absorption using ^{131}I-labelled triolein was normal. The absorption of folic acid (Chanarin, Anderson, and Mollin, 1958) was normal, the peak serum concentration being 56 μmg./ml. after an oral dose of 2.2 mg. of the vitamin. An ascorbic-acid-saturation test revealed a marked deficiency of the vitamin, the patient requiring 16 daily oral doses of 700 mg. to achieve saturation.

Eleven serial E.E.G.s were recorded in the period before the start of treatment with therapeutic doses of folic acid (Days 1–18, Fig. 2). None of the records showed the epileptic activity that had been seen three years before. However, the background activity now showed a moderate to severe non-specific generalized abnormality (Fig. 1B). There was marked polyrhythmia, a considerable excess of moderate-high-amplitude theta (4 to 7 cycles per second) and delta (under 4 cycles per second) waves, and poor reduction of this rhythmic activity when the eyes were opened.

Response to Treatment with Folic Acid

The haematological and clinical response to treatment is summarized in Fig. 2. An intravenous injection of 0.7 mg. of folic acid was given on the second and ninth days after admission in order to study its rate of clearance from the plasma (Chanarin, Mollin, and Anderson, 1958). Though this was followed by a small rise in the percentage of reticulocytes the marrow remained megaloblastic. The ascorbic acid was given during the same period.

Intramuscular injection of folic acid (30 mg. daily) was started on the nineteenth day. The *haematological response* was excellent. There was a reticulocyte response with a peak of 22% on the fifth day after the start of folic-acid therapy. The red-cell count rose rapidly and reached 4,000,000/c.mm. 30 days after the start of treatment. Aspiration of sternal marrow repeated 12 days after the start of folic-acid treatment showed that haemopoiesis was entirely normoblastic.

The *clinical response* was much less satisfactory. Two days after starting treatment with folic acid he began to have frequent minor epileptic attacks. These attacks consisted of jaw movements, upward deviation of the eyes, and plucking of the bedclothes. He became very vague and failed to respond to simple remarks. Each attack lasted for half an hour, and the attacks became increasingly more frequent during the next three days. He became incontinent of urine and faeces and extremely difficult to manage. The attacks were not influenced by increasing the dose of phenobarbitone to 390 mg. daily.

Nine E.E.G.s were recorded during the 10 days following the start of treatment with intramuscular folic acid. Each record now showed the changes diagnostic of epilepsy—namely, paroxysms of high amplitude, bilaterally symmetrical and synchronous polyspikes (Fig. 1C). There was no change in the moderate-to-severe background abnormality previously noted.

Subsequent Progress.—As the precipitation of epileptic attacks appeared to coincide with the administration of folic acid, treatment with this vitamin was stopped after seven days. Six days later his mental state showed considerable improvement, and the minor epileptic attacks again became infrequent and finally ceased. Four E.E.G.s recorded from the sixth to the eleventh day after stopping folic acid showed the disappearance of the paroxysmal polyspike/slow-wave activity, though the severe generalized abnormality was still present. There was also great

improvement in both his mental and his physical state, and he was discharged on 260 mg. of phenobarbitone daily 11 weeks after admission. His blood count at this time was: red cells, 4,900,000/c.mm.; Hb, 15.6 g./100 ml.; P.C.V., 48.5%. There were no abnormalities in the stained film.

Second Admission

The patient remained well during the next 16 weeks. However, a blood count at the end of this period showed the reappearance of macrocytes and also hypersegmentation of the neutrophils, and, as this finding suggested the return of megaloblastic haemopoiesis, he was readmitted for further study.

A blood count at this time showed: red cells, 4,300,000/c.mm.; Hb, 14.3 g./100 ml.; P.C.V., 46%; M.C.V., 107 cubic microns. Aspiration of sternal marrow showed the presence of intermediate megaloblasts and giant metamyelocytes. The serum vitamin B_{12} concentration was within the normal range, being 190 $\mu\mu$g./ml. He was therefore again suffering from a megaloblastic anaemia which required treatment with folic acid. Though our previous experience with folic acid in this patient had suggested that the drug might have precipitated attacks of epilepsy there was no definite evidence for a causal relationship. He was therefore given an intravenous injection of 0.7 mg. of folic acid to study its rate of clearance from the plasma, and this was followed the same day by an intramuscular injection of 15 mg. Twenty hours later he was again having repeated epileptic attacks, he had become stuporous, and he was incontinent of urine and faeces. An E.E.G. record taken before treatment with folic acid showed the generalized abnormality previously described but no evidence of epileptic activity. Twenty-four hours after readministration of folic acid the E.E.G. again showed the changes characteristic of epilepsy.

Folic acid was therefore withdrawn, the patient having received 60 mg. over a period of 48 hours. Phenobarbitone was also stopped and acetazolamide, 250 mg. twice daily, was substituted. On this regime his fits were completely controlled, and his E.E.G. showed not only no paroxysmal activity but a very marked improvement in the generalized background abnormality (Fig. 1D). A marrow aspiration repeated before discharge showed a return of normoblastic erythropoiesis.

His blood count five weeks after admission was: red cells, 5,200,000/c.mm.; Hb, 15.6 g./100 ml.; P.C.V., 49%. There were no abnormalities in the stained film.

Folic-acid Studies

As already mentioned, the rate of clearance of folic acid from the plasma after an intravenous injection of 15 μg./kg. body-weight (0.7 mg.) was studied before treatment on each admission. The results are shown in Fig. 3.

On his first admission, when the red-cell count was 1,200,000/c.mm., two tests were carried out. In both the rate of clearance was far more rapid than in normal subjects. The serum folic-acid levels three minutes after the injection in these two tests were 23 and 33 μmg./ml. respectively. In both tests the injected dose of folic acid was completely removed from the plasma by the time the 15-minute blood sample was taken.

On his second admission, when the red-cell count was 4,300,000/c.mm., the rate of clearance of injected folic acid was normal, the serum folic-acid levels 3, 15, and 30 minutes after the injection being 91, 25, and 14 μmg./ml. respectively.

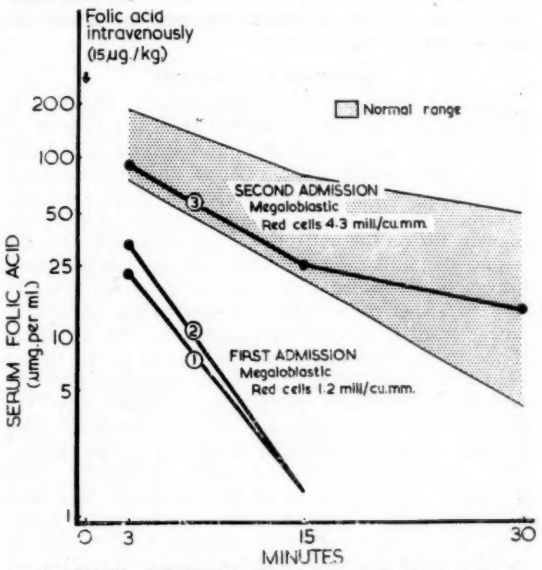

FIG. 3.—Results of folic-acid-clearance test during two admissions with megaloblastic anaemia.

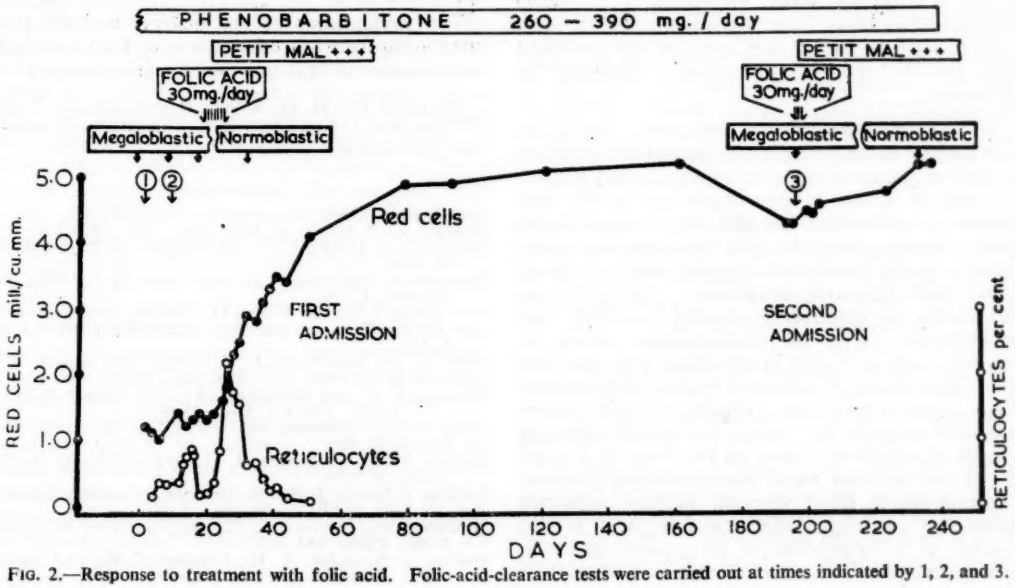

FIG. 2.—Response to treatment with folic acid. Folic-acid-clearance tests were carried out at times indicated by 1, 2, and 3.

Discussion

This patient presented with a megaloblastic anaemia which responded completely to treatment with folic acid. There was no evidence of vitamin-B_{12} deficiency and intestinal function appeared normal. Though he retained excessive amounts of ascorbic acid in a saturation test this failed to influence erythropoiesis. It therefore seemed likely that the megaloblastic anaemia was the result of the large doses of phenobarbitone he had been taking.

The administration of therapeutic doses of folic acid (30 mg. daily), however, though it produced an optimal haematological response, precipitated frequent epileptic attacks, and this occurred while he was still taking large doses of phenobarbitone. This effect is all the more remarkable because treatment of the megaloblastic anaemia which develops in patients receiving anticonvulsants is said to reduce the number of attacks (Hawkins and Meynell, 1958).

Pathogenesis of the Anaemia

There is evidence that megaloblastic anaemia in patients taking primidone may arise in the absence of both deficiency of vitamin B_{12} and folic acid (Chanarin, Elmes, and Mollin, 1958). Such an anaemia must presumably be due to an interference with folic-acid function. Phenobarbitone appears to act in a similar manner, for on the patient's second admission both the serum vitamin-B_{12} concentration and the rate of plasma clearance of injected folic acid were normal (Fig. 3). However, when the anaemia was severe (first admission), deficiency of folic acid was present, for the clearance of the injected vitamin from the plasma to the tissues was very rapid (Fig. 3). This suggests that the ineffective folic-acid metabolism induced by the presence of the barbiturate will, if continued long enough, result in folic-acid depletion of the tissues. The development of folic-acid deficiency after prolonged administration of an antagonist has been demonstrated by Broquist (1956) and by Hiatt, Goldstein, and Tabor (1958) in patients with leukaemia treated with the folic-acid antagonist methotrexate (amethopterin). Using the excretion of formiminoglutamic acid as an index of folic-acid deficiency (Silverman, Gardiner, and Bakerman, 1952), they showed that the haematological effect of the antagonist usually preceded evidence of folic-acid deficiency by many weeks.

Convulsant Action of Folic Acid

It is difficult to understand why therapeutic doses of folic acid precipitated epileptic attacks in this patient. The mode of action of phenobarbitone as an anticonvulsant is unknown. The fact that a megaloblastic anaemia requiring treatment with folic acid may occur in patients taking barbiturates suggests that these drugs interfere with folic-acid metabolism. However, one would hardly be justified in arguing therefrom that phenobarbitone exerts its anticonvulsant action by interfering with folic-acid metabolism, and that this anticonvulsant action is negatived by the administration of large doses of folic acid. Though this view cannot be excluded it would be a major assumption regarding the mode of action of a drug on the basis of a single case. If, on the other hand, phenobarbitone produces its anticonvulsant effect through another metabolic pathway the convulsant effect of folic acid is best explained as a by-product of its general effect on cellular metabolism. It is conceivable that when there is interference with folic-acid metabolism all cell function, including that of the cerebral cells, is depressed. Under these circumstances of depressed cell function the cerebral cells may be incapable of the massive simultaneous discharge which constitutes the epileptic attack, and this may only become possible when this interference has been overcome by adequate doses of folic acid.

Whatever the explanation, it is likely that the convulsant effect of folic acid is only possible under particular circumstances, for this action has not previously been demonstrated in patients with megaloblastic anaemia associated with anticonvulsant drugs. These special circumstances may be related to the severe generalized background abnormality in the E.E.G. This abnormality in the E.E.G. is non-specific and is found in a wide variety of conditions, which might be termed "toxi-metabolic" (Laidlaw, 1959). General electroencephalographic changes of the same type are usual in cases of pernicious anaemia with or without subacute combined degeneration of the cord (Walton, Kiloh, Osselton, and Farrall, 1954). In this patient the electroencephalographic changes were not due to the anaemia, since they persisted after the anaemia had been treated by adequate doses of folic acid. Furthermore, the abnormality was present only when he was taking large doses of phenobarbitone, and was much reduced when acetazolamide was substituted for phenobarbitone. Since phenobarbitone does not usually produce such a generalized abnormality, it would seem possible that this patient showed a cerebral sensitivity to the drug. This unusual sensitivity to the action of phenobarbitone in an epileptic may have produced the special circumstances under which administration of folic acid had a convulsive effect.

Summary

The case is described of a patient who presented on two occasions with megaloblastic anaemia while taking large doses of phenobarbitone.

Treatment with folic acid (30 mg. daily) produced an optimal haematological response, but on each occasion was associated with the precipitation of frequent minor epileptic attacks.

The pathogenesis of the anaemia and the possible relationship between treatment with folic acid and the precipitation of epileptic activity are discussed.

We thank Dr. M. D. Milne for permission to study this case and Miss J. Pope, Miss B. B. Anderson, and Miss A. M. Lees for technical assistance.

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TREATMENT OF FUNCTIONAL MENSTRUAL DISORDERS WITH NORETHISTERONE

BY

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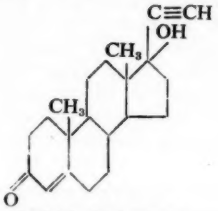
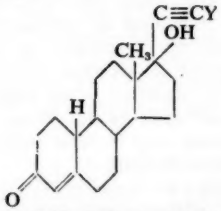
The introduction of 19-nortestosterone derivatives (Djerassi *et al.*, 1954) has put a series of powerful oral progestogens at the disposal of the clinician, whereas previously the only orally active progestogen available was ethinyltestosterone (ethisterone). The corresponding nor-compound, ethinyl-nortestosterone (see Formulae), was found by Hertz *et al.* (1954) to be five times as active by the Clauberg (1930) test, when given by the oral route to rabbits.



17α-Ethinyltestosterone (Ethisterone)



17α-Ethinyl-19-nortestosterone (Norethisterone)

Greenblatt (1956) studied the progestogenic properties of norethisterone. He found that in doses of 10 mg. daily for five days it would induce withdrawal bleeding in women complaining of amenorrhoea, provided the endometrium was adequately primed with oestrogens, and that it raised the basal body temperature significantly in doses of 10 to 30 mg. daily. Pots (1957) was able to transform the endometrium of an oestrogen-primed castrate and of amenorrhoeic women into a fully secretory type with doses of 10 to 20 mg. daily for 10 days and to induce luteal changes in the vaginal smears as well as to demonstrate a marked thermogenic effect. He also induced a withdrawal bleeding in oestrogen-primed amenorrhoeic patients with a total dose of 40 mg. given over a period of two to four days.

The 19-nortestosterone compounds are not only powerful progestogenic agents but also potent inhibitors of pituitary gonadotrophic activity (McGinty and Djerassi, 1958), and the most publicized use to which they have been put in this connexion is to act as oral contraceptives by suppressing ovulation (Pincus *et al.*, 1958). It is, nevertheless, difficult to demonstrate the inhibition of ovulation objectively in women treated with these compounds because they exert their progestational properties shortly after the administration is begun. It is, however, generally agreed that spasmodic dysmenorrhoea occurs only in an ovulatory cycle and can be prevented from ensuing in a cycle in which ovulation has been inhibited (Sturgis and Albright, 1940). If the 19-nortestosterone compounds suppress ovulation dysmenorrhoea should not occur provided they are administered from an early date in the cycle.

With these properties in mind we set out to study the following effects of norethisterone ("primolut N"). (1) The ability to induce withdrawal bleedings in cases of metropathia haemorrhagica when given once a month, thereby forestalling the otherwise inevitable metropathic bleeding phase. (2) The ability to arrest haemorrhage when given during the course of a metropathic bleeding episode. (3) The ability to induce normal menstrual loss in cases of ovulatory menorrhagia. (4) The ability to prevent dysmenorrhoea.

Norethisterone was administered to 75 women during the course of 349 menstrual cycles in doses varying between 5 and 25 mg. daily.

Production of Withdrawal Bleeding

Albright (1938) suggested the device of inducing a "medical curettage" once a month in cases of anovulatory metropathic bleeding so that the endometrium should not be given the opportunity of building itself up to the histological picture of cystic glandular hyperplasia from which another episode of prolonged and sometimes heavy metropathic bleeding could be expected to occur. Before the introduction of the 19-norsteroids it had been our custom to give either progesterone 25 mg. daily by injection for four days or ethisterone 25 mg. daily by mouth for 10 days to achieve the withdrawal bleeding.

A total of 35 patients suffering from metropathia haemorrhagica were given norethisterone to produce withdrawal bleeding. The diagnosis was either confirmed by finding the condition of cystic glandular hyperplasia on histological examination of the curettings, or assumed from the previous pattern of the menstrual bleeding. In all, 182 courses were administered, each course lasting for four days, except for four of three days' duration and another in which the tablets were given for 10 days. The daily dose was 25 mg. in 62 courses and 20 mg. in 45, 15 mg. in 38, 10 mg. in 34, and 5 mg. in 3. On every occasion except two, withdrawal bleeding duly occurred within a few days of the last dose. The failures took place once when the daily dose was 20 mg., though this patient responded on four other occasions to a similar dose; and once when 5-mg. doses were administered. Three patients complained of nausea. In one of these a 25-mg. daily dose was associated with nausea, but when the dose was lowered to 20 mg. the symptom disappeared, though it reappeared later on 10-mg. doses. A second patient complained of nausea only with the sixth and seventh course of treatment using 20-mg. doses. One patient complained of feeling bloated when taking 20 mg. daily.

Haemostasis

There were only eight opportunities to use norethisterone in an attempt to arrest bleeding during a metropathic episode. Pots (1957) found that 10 or 20 mg. daily checked the bleeding significantly within 24 or 48 hours. He continued the treatment for up to 5, 6, or 10 days, withdrawal bleeding taking place on the third or fourth day after treatment was discontinued. Endometrial biopsy revealed secretory changes after a total dose of 100–200 mg. had been given.

Our regime was to give 20 mg. daily for four days and then to "taper off" by giving 10 mg. daily for a subsequent seven days, so that a total dose of 150 mg. was administered. This proved successful on five out of the eight occasions, though in one of these five cases the

tapering-off dose was 15 mg. In the other three cases the treatment failed to arrest the haemorrhage.

Induction of Normal Bleeding in Cases of "Menorrhagia"

There are two main types of bleeding pattern in cases of functional uterine haemorrhage. The first is metropathic, in which periods of amenorrhoea of variable duration alternate with bleeding episodes. Ovulation does not take place and the endometrium hypertrophies under the unopposed influence of oestrogen and gives rise to the histological picture of cystic glandular hyperplasia and the clinical pattern of prolonged bleeding varying in amount from a mere trickle to a flooding when the endometrium eventually breaks down.

In contrast, there is the picture of ovulatory menorrhagia, in which bleeding recurs at fairly regular intervals, though the cycles may be shorter than usual. The bleeding is heavy and may last for seven days or more. Basal temperature records often indicate that ovulation has taken place. Tyler (1957) has studied a number of such short cycles by means of basal temperature records, pregnanediol estimations, cervical and vaginal smears, and endometrial biopsy, and concludes that the luteal phase is curtailed and that this may be a cause of infertility. It may also lead to excessive bleeding owing to inadequate progesterone influence on the endometrium. Administration of 19-nortestosterone compounds might be expected to induce full secretory changes and therefore give rise to normal shedding and normal menstrual loss.

Norethisterone was administered from the 15th to 25th days in a total of 52 cycles in 13 patients suffering from menorrhagia. The subsequent menstrual bleeding was normal in amount, instead of being heavy, in 34 of these cycles (13 out of 20 on a daily dose of 20 mg., in all 8 cycles on 15 mg., in 13 out of 22 on 10 mg., and in neither of the 2 cycles on 5 mg.), "break-through" bleeding occurred on one occasion with the 20-mg. dose and on another with the 10-mg. dose. Dysmenorrhoea was complained of, however, in 8 and possibly 10 of the 20 cycles treated with 20 mg. daily, in 5 of the 8 cycles treated with 15 mg., and in 5 and possibly 6 of the 22 cycles treated with 10 mg. In only one of the patients involved was dysmenorrhoea a prominent feature of the menstrual pattern before treatment. In this case two and possibly four cycles on a 20 mg. dose were associated with dysmenorrhoea, though one period on the 10 mg. dose was painless but heavy.

Painless Periods after Norethisterone Therapy in Cases of Dysmenorrhoea

Twenty-seven patients suffering from incapacitating spasmodic dysmenorrhoea accompanying every period were treated with norethisterone in a total of 107 cycles.

Results of Norethisterone Treatment of Spasmodic Dysmenorrhoea

Daily Dosage	Painless	Painful	Break-through Bleeding	
25 mg.	2	2		
20 ,,	21	7	1	Also with pain
15 ,,	10	2	2	One cycle also with pain
10 ,,	26	7	3	,, ,,
7·5 ,,	5	2		
5 ,,	1		1	
	65	20	7	

The usual course consisted in giving norethisterone daily for 20 days from the 5th to the 25th day of the cycle in doses varying from 5 to 25 mg. This regime was adopted in 91 cycles (85%), though in one case the treatment was administered from the 4th to the 24th day, and in two others from the 6th to the 26th day. The dosage, number of cycles, and the results are given in the Table.

Case 1.—This patient had been under our care for many years. It took over a year to explain the importance of paying attention to the "timing" of hormone administration, and we were beginning to despair of ever training her, when she suddenly conformed to the necessary discipline, and from then on for three years stilboestrol 2 mg. daily for 14 days, starting within the first five days of the cycle, kept her painless and content. With the advent of the new progestogens she was given "enavid" with disastrous results, which were repeated when norethisterone was substituted. She accounts for one of the two painful cycles listed under 25 mg. in the Table and for two of the painful cycles under 20 mg. and for the break-through bleeding on the 20-mg. dose.

The number of cycles treated was not sufficient to reach a conclusion concerning the minimal or optimal daily dose, though if the two painful cycles experienced on the 20 mg. dose in Case 1 are subtracted there would be 5 painful as opposed to 21 painless cycles on that dose (80% success), as compared with 7 painful as against 26 painless cycles on the 10-mg. dose (about 79% success). This suggests that the 10-mg. dose is as effective as the 20-mg. dose. Individual patients of course vary in their response to the hormone. This is shown in Case 2.

Case 2.—In two out of three cycles this patient experienced pain when treated with the 10-mg. daily dose, whereas in eight cycles on a 15-mg. daily dose painless bleeding ensued.

On 13 occasions the treatment was continued for less than 20 days: three times on 15-mg. doses for 10 days with painful results; twice on 10-mg. doses for 14 days, the subsequent periods being painless; on three occasions when only 5-mg. doses were given for 14 days pain occurred; in three cycles 10-mg. doses were given for 10 days and pain ensued; in one cycle break-through bleeding occurred after seven days with a daily dose of 10 mg.; and in another cycle break-through bleeding occurred on the 10th day of a 5-mg. daily course. Thus, though it may sometimes be possible to induce a pain-free period after a 14-day course, it seems that a 20-day course is more likely to give good results.

On five occasions the treatment was begun later than the sixth day of the cycle, with the result that the ensuing period was painful. The daily dose in three of these cycles was 15 mg. and in the other two 10 mg.

Side-effects were not a conspicuous feature. One patient took norethisterone in 15-mg. daily doses for one cycle only, and said it made her feel "peculiar," and another patient developed severe acne after she had been taking 10 mg. daily for 20 days in 12 consecutive cycles.

Discussion

These studies of the effects of norethisterone have been carried out in a routine gynaecological endocrine clinic. On the one hand, it is difficult to persuade patients attending such a clinic to submit to a battery of investigations such as pre- and post-treatment endometrial biopsies: indeed, in many cases it is impossible to train the patients to record their basal body temperatures accurately. On the other hand, in a busy clinic

of this kind it is difficult to provide the facilities and assistance to carry out such investigations. Our object, therefore, was to determine the therapeutic efficacy on a relatively large number of cases submitted to the ordinary routine of hospital out-patient treatment, rather than to study a small and carefully selected number of patients who would be willing to submit to the inconvenience of time-consuming controls and investigations. Basal temperature records, vaginal cytological studies, and endometrial biopsies have been performed in some of these cases, but the results of these studies have not been included, because they are inadequate to affect the overall clinical impression. This is not a carefully controlled double-blind trial; it is an attempt to evaluate the behaviour of a new therapeutic compound in a routine clinic.

From the results obtained it seems clear that a four-day course of norethisterone in daily doses of 10 mg. or more will consistently induce withdrawal bleeding, simulating a normal period, when given monthly in cases of metropathia haemorrhagica. It may even be capable of doing so in lower doses. From the evidence available in the literature these withdrawal bleedings are brought about by converting the proliferative endometrium which has been under the constant and sole influence of oestrogen into a secretory type which sheds like that of a normal ovulatory cycle when the progestogen influence is withdrawn. This represents a valuable method of tiding a patient over a phase of non-ovulatory ovarian activity in the hope that spontaneous ovulatory cycles will eventually be re-established.

Only eight opportunities occurred to test the haemostatic efficacy of a regime which consisted of four daily doses of 20 mg. of norethisterone followed by a week's tapering off on 10 mg. daily. This regime was effective on five occasions. Perhaps the higher doses should have been continued for longer than four days or that even higher doses than 20 mg. should have been given initially.

The treatment of ovulatory menorrhagia with progestogens probably calls for more intensive studies than were possible here. Basal temperature records and vaginal cytology might be employed to pin-point the day of ovulation and endometrial biopsies, on the first day of the period, to demonstrate that bleeding is taking place from an inadequately luteinized endometrium. A further endometrial biopsy after treatment might establish the fact that the progestogen had in fact induced full maturation of the endometrium, though it might prejudice the evaluation of the effect of the progestogen on the volume of bleeding. Single- or double-blind trials with progestogen might help to elucidate the extent of relief of this predominantly subjective end-result—namely, the amount of blood actually lost at each menstrual haemorrhage. These would be formidable studies, and would occupy the resources of even the best-stocked endocrine clinic for many months, if not years. Our results suggest that when norethisterone is administered in 10-mg. doses and upwards daily from the 15th to the 25th day of the cycle the subsequent bleeding is "normal" instead of "incapacitating" in amount in two-thirds of the cycles treated. These results are much better than those obtained, in our experience, with androgens or with ethisterone.

An interesting side-effect, however, appears as the result of giving the progestogen in the second half of the cycle—dysmenorrhoea. Patients volunteered the information that their periods were painful in 16 and possibly 19 of the 50 cycles treated. The progestogen therefore produced pain in 33% to almost 40% of the cycles treated. In no case was the dysmenorrhoea so severe as to make the patient unwilling to continue with the treatment, though in some cases the failure to modify the bleeding, combined with the fact that treated cycles were painful, led to the treatment being abandoned. Sturgis and Albright (1940) drew attention to the fact that spasmodic dysmenorrhoea occurs only in ovulatory cycles, and it would seem to be due to progesterone. Administration of a highly potent progestogen in the second half of the cycle might therefore be expected to induce dysmenorrhoea in some cases.

On the other hand, if this powerful progestogen is also a suppressant of pituitary gonadotrophic activity when given early in the cycle one would expect that it would lead to painless periods in cases of dysmenorrhoea. This was the result achieved in 75% of 107 cycles treated.

Summary

Norethisterone ("primolut N") was given to 75 women suffering from functional menstrual disorders, during the course of 349 cycles, the doses varying from 5 to 25 mg. daily.

It succeeded in inducing withdrawal bleeding in 180 out of 182 occasions in cases of metropathia haemorrhagica. It seems likely that the dose need not exceed 10 mg. daily for four days, and may even be lower.

On five out of eight occasions a dosage of 20 mg. daily for four days, then 10 mg. daily for seven days, arrested a phase of metropathic bleeding and was followed by a normal withdrawal bleeding.

When administered from the 15th to the 25th day of the cycle in 13 cases of ovulatory menorrhagia, normal bleeding was substituted for the heavy loss in 34 out of 52 cycles. Dysmenorrhoea was complained of, however, in 18 and possibly 21 of the 52 cycles.

Painless periods followed administration of norethisterone on 65 out of 91 occasions in 27 patients complaining of dysmenorrhoea. When the treatment was begun after the sixth day of the cycle the ensuing period was always painful.

Side-effects were not conspicuous. One patient developed acne after taking 10 mg. daily for 20 days in 12 consecutive cycles, and 3 of the 35 patients being treated with metropathia complained occasionally of nausea.

We are grateful to Dr. Jürgen Friebel, of Schering A.G., Berlin, for placing unlimited supplies of primolut N at our disposal in order to enable us to undertake this clinical study. We are also grateful to Mr. G. S. Blackie, of Pharmethicals, London, for arranging for the supplies to be delivered to us.

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IMPORTANCE OF ASPIRIN AS A CAUSE OF ANAEMIA AND PEPTIC ULCER IN RHEUMATOID ARTHRITIS

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Few would question the value of aspirin (acetylsalicylic acid) in the treatment of rheumatoid arthritis. Carefully controlled trials (Empire Rheumatism Council, 1957; Medical Research Council and Nuffield Foundation, 1957) have shown little difference between the therapeutic effect of aspirin and cortisone in the long-term management of this disease.

A number of reports have been published which suggest that aspirin may be an important cause of gastro-intestinal bleeding. Douthwaite and Lintott (1938) reported that aspirin can cause anaemia, and showed by gastroscopy that it had an irritant action on the gastric mucosa. Their conclusions were questioned by Paul (1943), who observed no aspirin effect in 1,000 gastroscopies. In a further study of the effects of aspirin, Douthwaite (1954), using a slightly different method, found a positive flare reaction in 17 out of 37 patients taking ordinary aspirin but no gastric irritation in 12 patients taking soluble aspirin.

Muir and Cossar (1955) studied the effect of aspirin in patients with peptic ulcer. They found that administration of aspirin to patients with radiological evidence of peptic ulcer was followed by increased gastric secretion and the appearance of occult blood in the stools. A study of gastrectomy specimens from patients who had been given aspirin shortly before operation showed mucosal irritation in 12 out of 20 given aspirin but in only 2 out of 20 given calcium aspirin. They found the incidence of dyspepsia in 300 controls taking aspirin to be 5% compared with 33% in 318 patients known to have peptic ulcers. Of 83 such patients having frequent exacerbations of symptoms 33 had taken aspirin within 24 hours, and 8 of these blamed aspirin for their symptoms. They also found 15 patients with chronic dyspepsia which subsided when aspirin was withdrawn. A further analysis of the histories of 166 patients admitted with haematemesis revealed that 30% had taken aspirin within six hours of the haemorrhage. In a group of patients with acute haemorrhages but without previous symptoms, this rose to 50%. Among patients entering hospital for other reasons only 5% had consumed aspirin within six hours of admission. Muir and Cossar (1959) again found that 57 out of 106 patients admitted with gastro-duodenal haemorrhage had taken aspirin within 48 hours of their initial bleed, compared with 17% in a group of 106 admitted for other reasons.

Kelly (1956) reviewed the literature and reported three cases with repeated gastro-intestinal haemorrhage related to aspirin consumption which did not recur when aspirin was avoided. Schneider (1957) found that ordinary aspirin led to the appearance of occult blood in gastric secretions, while calcium aspirin did not. Lange (1957) reported persistent occult blood in the stools of patients taking aspirin, though it occurred less often with coated aspirin and when the tablets were taken with meals. He also found that 45% of 96 patients with gastro-intestinal haemorrhage had taken salicylates prior to admission. Alvarez and Summerskill (1958) considered that the taking of salicylates was a precipitating factor in 40% of 103 patients admitted for massive gastro-intestinal bleeding. They found that the incidence of radiologically proved ulcers in this group was low, suggesting that haemorrhage had occurred from acute lesions. They demonstrated occult blood in the stools of 50% of healthy individuals, patients with peptic ulcers, and patients with dyspepsia who had taken either soluble or insoluble aspirin by mouth. They found no evidence that soluble aspirin reduced the risk of major bleeding, and no relationship between the method of taking salicylate preparations and the occurrence of haematemesis and melaena. In a further paper (Summerskill and Alvarez, 1958) they reported two cases of severe anaemia in patients who had taken large amounts of salicylates. After a substantial reduction in dose there was no recurrence of anaemia for periods of 7 and 10 months.

Stubbé (1958) found that 70% of 140 patients admitted with rheumatic complaints and also 70% of 40 healthy controls who took aspirin had occult blood in their stools. Bleeding was unrelated to dyspepsia, dose, or mode of administration of the drug. Porter, Lewis, and Dixon (1959), using red cells tagged with ^{51}Cr, estimated a loss of blood which was usually less than 5 ml. daily in all 11 subjects taking either aspirin or calcium aspirin. This loss was diminished or absent when enteric-coated aspirin was substituted.

On the basis of this evidence it has been suggested that aspirin is a potentially harmful drug, and extravagant claims have been made on behalf of a number of other analgesics whose value in the treatment of rheumatoid arthritis has never been assessed by controlled trials and whose potential side-effects during long-term administration are not yet clearly known. The evidence that aspirin causes bleeding from the gut must be accepted, but it is entirely possible that many other drugs not yet tested may have a similar effect. In any case, such chronic loss of blood is only of importance if it is of a magnitude sufficient to decrease iron stores to an extent likely to cause anaemia.

In view of the possibility that the reputation of an exceedingly useful drug might suffer unnecessarily, it was decided to study the variations in haemoglobin levels in a large group of patients with rheumatoid arthritis, most of whom had been taking aspirin continuously or intermittently in varying doses for a number of years.

Materials and Methods

The case records of 244 patients suffering from rheumatoid arthritis admitted between June, 1948, and July, 1951, to the rheumatism unit of the Northern General Hospital, Edinburgh, were studied. The composition of the group is shown in Table I. The progress of this group since discharge from the hospital has already been reported in detail by Duthie, Brown, Knox, and Thompson (1957). Haemoglobin levels were measured colorimetrically by the alkali-haematin method of Clegg and King (1942), with 100% haemoglobin equal to 14.8 g./100 ml. The mean levels of haemoglobin for the whole group on admission, at discharge, and at approximately two, four, and six years thereafter were

TABLE I.—*Composition of the Group*

Data	Males	Females	Total
No. of cases of rheumatoid arthritis admitted between June, 1948, and July, 1951			307
Period between discharge and final assessment (months)	67·4 (range 52 to 92 months)		
No. of deaths between discharge and final assessment	14	22	36
No. no longer available			27
,, available at final assessment	62	182	244
Mean age at third assessment	54·1	55·3	
Mean duration of disease at third assessment (6 years)	11·3	12·5	

determined. A more detailed study was made of those patients in whom the haemoglobin level had varied by more than 20% during the period under review. Detailed information was sought about the incidence of dyspepsia and peptic ulceration.

Results

Table II shows the mean haemoglobin levels of the whole group on admission, at discharge, and at approximately two, four, and six years thereafter. The great

TABLE II.—*Changes in Mean Haemoglobin Levels Between Admission and Third Assessment*

	Whole Group (244)	Adequate Salicylates (75)	Nil or Occasional Salicylates (31)
Admission	82·7 ±17·68	83·0	87·2
Discharge	86·7	85·0	90·9
First assessment	82·4	82·0	86·4
Second ,,	79·6	79·6	82·8
Third ,,	92·4 ±10·84	92·1	97·4

majority of the patients were on regular aspirin, but in many cases the exact dosage was not known. To overcome this possible bias 75 patients known to have taken regularly at least 40 gr. (2.6 g.) and usually 60 gr. (3.9 g.) of aspirin daily were compared with 31 patients known to have taken none or only very occasional doses of salicylates. It can be seen that there has been an overall gain in the mean haemoglobin level of the group after six years, and also that the group on adequate salicylates throughout this time showed a similar increase in mean haemoglobin level to that of the group on none or only very occasional doses of the drug.

TABLE III.—*Variations in Haemoglobin Levels Between Admission and Third Assessment in 244 Cases*

Final haemoglobin within 20% of admission level	185 (75·8%)
Rose 20%	55 (22·6%)
Fell 20%	4 (1·6%)

Table III shows the variations in the haemoglobin level of the whole group: 75.8% remained at or about the same level; in 22.6% the mean haemoglobin rose more than 20%; and only four patients (1.6%) showed a drop of over 20%.

TABLE IV.—*Incidence of Dyspepsia in 244 Cases*

Dyspepsia noted	30 (12·3%)
Peptic ulcers (before admission, 7; after admission, 3)	10 (4·1%)
Other causes (ulcerative colitis, 2; chronic cholecystitis, 2; hiatus hernia, 2)	6 (2·5%)
No cause found	14 (5·7%)

Table IV shows that 30 patients (12.3%) complained of dyspepsia, troublesome enough to be noted on the case sheet. In only 10 patients (4%) was there clinical or radiological evidence of peptic ulcer. Six other patients had gastro-intestinal lesions which could contribute to dyspepsia, leaving 14 subjects (6%) with unexplained dyspepsia.

At the final assessment the haemoglobin was below 80% in 27 patients (11%). In only three of these was there evidence of peptic ulcer. Other diseases that might have a bearing on the anaemia were present in 12 instances, but in the majority the cause was undoubtedly rheumatoid arthritis in an active phase.

Discussion

Reports have appeared in the literature of the persistence of occult blood in the stools of patients taking salicylates, but from the results of the present study it is clear that it is of little importance as a cause of anaemia in patients with rheumatoid arthritis who have taken the drug over a period of years.

Further evidence against the idea that salicylates are an important cause of anaemia is provided by comparing the progress of a small group of patients who were not taking regular aspirin with another small group who were taking regular and adequate doses of the drug. The group not requiring aspirin (Table II) started with a higher haemoglobin level and gained in about the same proportion as the group on regular doses. These two groups, though probably differing in the activity of their disease, showed an equal gain after six years, providing further evidence of the unimportance of the minimal blood loss due to aspirin.

Table III shows the variations in haemoglobin levels throughout the period of study: 75.8% of the subjects remained at or about the same level; and 22.6% had an increase of over 20% in their haemoglobin level. In 65% of those whose haemoglobin rose oral or parenteral iron was known to have been given. Only four patients (1.6%) showed a fall of over 20%. Of these, one had a definite ulcer, one was found to have pernicious anaemia, and in one the disease was very active. The fourth patient had a low haemoglobin level recorded on one occasion which subsequently returned to normal.

Analysis of the whole group (Table IV) showed that 30 patients (12.3%) had suffered from dyspepsia. This compares with an incidence of 5% in 300 people representing an average cross-section of the community reported by Muir and Cossar (1955). Included in this group of 30 dyspeptics were 10 patients (4%) with clinical or radiological evidence of peptic ulcer. Only three (1.2%) developed their ulcer during the period of observation. Six of the remaining dyspeptics had other causes for their symptoms, but there were 14 patients (6%) in whom a definite diagnosis of ulcer could not be made. The incidence of definite ulcer in this series is a little under 5%, and if it is presumed that all 14 cases of unexplained dyspepsia had ulcers as well, this would mean an incidence of about 10%. Other estimates of the incidence of peptic ulcer in the general population vary from 5% to 15% with most authors, suggesting an overall incidence of around 10% (Harrison, 1950; Ivy, Grossman, and Bachrach, 1950; Doll and Jones, 1951; Sandweiss, 1951). A previous study on patients with rheumatoid arthritis (Short, Bauer, and Reynolds, 1957) revealed a frequency of 5.6% in 650 patients with rheumatoid arthritis. It would thus appear that, even if the majority of patients with unexplained dyspepsia are accepted as also having ulcers, there is no good evidence that aspirin causes an increased incidence of peptic ulcer in patients with rheumatoid arthritis.

In the analysis of patients with a final haemoglobin level below 80% a number of factors might have

contributed to the low level, but in only three of this group was there any suspicion of ulcer, and in only one was this confirmed radiologically. Nine patients were severely debilitated, and the low haemoglobin in the other six may have been related to disease activity, though a silent ulcer or gastro-intestinal haemorrhage cannot be excluded.

Conclusion

A study of 244 patients with rheumatoid arthritis followed for about six years has been made with particular reference to their intake of salicylates, haemoglobin levels, and the incidence of dyspepsia or ulcer. The great majority were on regular doses of aspirin.

Over the six-year period the group showed a significant increase in haemoglobin level. A smaller group not on regular aspirin showed a comparable increase.

Only three patients (1.2%) were known to have developed clinical or radiological evidence of peptic ulcer while on aspirin. Seven other patients had or were suspected of having an ulcer before they developed rheumatoid arthritis.

The incidence of peptic ulcer in this series compares favourably with that in the general population.

It is concluded that the great majority of patients with rheumatoid arthritis can tolerate regular aspirin without an increase in anaemia. The dangers of causing peptic ulceration or precipitating gastro-intestinal haemorrhage appear to have been greatly exaggerated.

During the period when this work was done, one of us (F. D. B.) was supported by a Research Fellowship from the Canadian Arthritis and Rheumatism Society, and the Rheumatic Diseases Unit was in receipt of grants from the Nuffield Foundation, Medical Research Council, and Boots Pure Drug Company Limited.

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The National Marriage Guidance Council has recently issued a new publication, *Starting Your Family* (price 2s. 6d.). It includes advice on planning, on financial, medical, routine, and personal topics, and on infertility. There is an appendix on contraceptive methods, and a list of recommended books. Revised editions of *All About Your Wedding* and *The L.S.D. of Marriage*—both priced at 2s. 6d.—are also available. All three booklets may be obtained (3s. each post free) from the Book Room, 78, Duke Street, London, W.1.

FULMINATING AND FATAL PNEUMONIA AND SEPTICAEMIA DUE TO ACHROMOBACTER ANITRATUS

BY

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Achromobacter anitratus was first described by Schaub and Hauber in 1948. Since then several authors have isolated this organism from patients with various illnesses, but without convincing proof of its pathogenicity. The following report gives evidence that the organism may be highly pathogenic.

Case History

A man aged 50 had had chronic bronchitis for ten years. In 1956 he had lobar pneumonia and recovered slowly but satisfactorily. He remained well until October 24, 1957, when he felt abnormally tired but noticed nothing else. At 2 a.m. on October 25 he was awakened by a rigor; he felt progressively feverish and unwell and began to cough up pink froth. He complained of pleuritic pain over the anterior and upper part of the left side of the chest. His condition gradually deteriorated, and when seen by his family doctor at 1 p.m. the same day he was cyanosed and orthopnoeic; his temperature was 100° F. (37.8° C.) and the pulse very weak.

He was admitted to hospital at 5 o'clock the same evening and was obviously very ill, distressed, and confused, with central cyanosis and marked tachypnoea. The pulse volume was poor, the rate 100, and the blood-pressure 110 mm. Hg systolic and 70 mm. diastolic. The percussion note was impaired over the left upper lobe anteriorly and there was bronchial breathing with medium crepitations in the same area. Medium crepitations were also heard over both lower lobes. The white cell count was 13,200/c.mm. (77% polymorphonuclear neutrophils, 3% eosinophils, 5% monocytes, and 15% lymphocytes), and the haemoglobin 98% (14 g./100 ml.). A diagnosis of fulminating lobar pneumonia was made. The probable pathogenic organism was thought to be *Staphylococcus aureus*, which had often been found in similar cases at this time during the epidemic of Asian influenza. Penicillin 250,000 units and streptomycin 0.25 g. were given intravenously at once, and 3 million units of penicillin with 0.5 g. of streptomycin intramuscularly and repeated every two to three hours.

An hour after admission the patient's condition had further deteriorated, and both the cyanosis and the dyspnoea had greatly increased. The systolic blood-pressure had fallen to 90 mm. Hg, the diastolic being unrecordable. An intravenous drip of glucose-saline was set up, and by this means 5 mg. of noradrenaline was rapidly given. Hydrocortisone 100 mg. was also given intravenously, and erythromycin 1 g. by mouth. The blood-pressure returned to 110/70 mm. Hg for a few minutes, but it quickly sank again to unrecordable levels although a total of 20 mg. of noradrenaline was given during the next six hours. His condition continued to deteriorate rapidly; he became comatose, and at 2.15 o'clock the next morning he died, 24 hours after the initial symptoms.

Bacteriology

Smears from a specimen of sputum examined on admission to hospital showed the presence of numerous Gram-negative diplococci morphologically indistinguishable from *Neisseria*. Cultures of the sputum on horse-blood agar, incubated for 24 hours at 37° C., gave a heavy growth of shiny, smooth, convex, circular colonies with an entire edge. The diplococci were encapsulated and non-motile. The biochemical reactions are given in the accompanying Table. The organism was finally identified at the Central Public Health Laboratory, Colindale, as a strain of *A. anitratus* (Schaub and Hauber) Brisou.

Biochemical Reactions of the Present Strain Compared with Those of A. anitratus (Schaub and Hauber) Brisou

Organism	Motility	Lactose	Glucose	Sucrose	Xylose	Mannite	Indole	Methyl Red	Voges-Proskauer	Citrate	Nitrates	Urease	Milk Plus B.C.P.
Present strain	–	–	A	–	A	–	–	–	–	+	–	+	A clot 12 days
A. anitratus	–	–	A	–	–	–	–	+	–	+	–	+	A clot 5–10 days

The organisms were resistant to 1 unit of penicillin per ml. of 2% blood agar, 10 μg. of chloramphenicol per ml., 1 μg. of streptomycin per ml., and 1 μg. oxytetracycline per ml., but sensitive to 10 mg. of sulphathiazole per 100 ml.

Gram-negative kidney-bean-shaped diplococci were seen in smears from bronchial pus obtained at necropsy but attempts to isolate the organism on culture failed owing to a heavy growth of *Escherichia coli*.

Post-mortem Examination (10 Hours After Death)

The body was that of well-nourished middle-aged male. Emphysematous bullae lay on the external surfaces of both lungs. Small amounts of fibrin were scattered over the pleural surface covering the left lung. Much of the left lower lobe and part of the left upper lobe were consolidated, red-grey, and airless. There were no deposits of fibrin upon the pleura covering the right lung. The right upper, middle, and lower lobes were severely congested, but consolidation was not complete.

Microscopically, the consolidation of the left lung was found to be due to a confluent haemorrhagic bronchopneumonia. In the most severely affected parts of the left lung the alveolar walls were damaged or distorted, and the capillaries distended with red cells, many of which had escaped into the alveolar spaces. Within the alveoli in this part of the lung were large numbers of polymorphonuclear leucocytes. Many small Gram-negative diplococci lay both inside the polymorphonuclear leucocytes and free within the alveoli; no other organisms were seen. The Gram-negative diplococci were most frequent in those parts of the lungs which were consolidated; a few were present in the left upper lobe and in the right lung.

The liver was pale and fatty; there was centrilobular congestion. The spleen was small and firm, with a well-preserved purple-red cut surface. Within many splenic leucocytes were Gram-negative diplococci. Both kidneys were the site of severe congenital cystic disease. Small scattered haemorrhages were present in the cortex of both adrenals, and among the disrupted cortical cells were many Gram-negative diplococci. The bone-marrow showed normal active haemopoiesis. The remaining organs showed no significant abnormality.

The cause of death was therefore considered to be confluent left haemorrhagic bronchopneumonia due to infection with Gram-negative diplococci, and accompanied by septicaemia with small adrenal cortical haemorrhages.

Discussion

The case reported is one of bronchopneumonia with septicaemia which proved fatal within 24 hours. The predominant organism isolated in culture from the sputum was *A. anitratus* (Schaub and Hauber) Brisou. Organisms with identical morphology were also seen in tracheal pus and intracellularly in histological sections from the lung, spleen, and adrenals. It seems, therefore, that the fatal infection in this patient was due to *A. anitratus*. Schaub and Hauber (1948) showed that this bacterium could be pathogenic for mice and guinea-pigs. In humans, such proof has been lacking. *A. anitratus* has been isolated in patients with urinary and with pulmonary infections, but its significance in these has not been clear (Schaub and Hauber, 1948). It has been found in the blood of patients suffering from fever and diarrhoea (Stuart *et al.*, 1949). Waage (1953) isolated it in a case of cerebral abscess but could not determine whether it was a pathogen or a saprophyte. It has also been found in patients with conjunctivitis (Moor, 1949). In none of these papers was there convincing evidence that *A. anitratus* had behaved as a pathogen. The case we have described above shows that *A. anitratus* may cause a severe and fatal illness with septicaemia and adrenal apoplexy.

It is obscure why this organism has not been clearly recognized before in cases of pneumonia. The fulminating onset in our patient was similar to that of certain cases of influenza so often met at the time, and an actual infection with the influenza virus may have favoured invasion by *A. anitratus*. No virus studies were done in our patient, but the widespread massive invasion by *A. anitratus* that we have demonstrated shows that this organism was ultimately responsible for the pneumonic, septicaemic, and adrenal manifestations. Chronic bronchitis and severe polycystic disease of the kidneys may also have been predisposing factors. *A. anitratus* has been described as particularly sensitive to the tetracyclines and less sensitive to streptomycin and sulphathiazole (Brooke, 1951; Lund, 1954). The organism we have described was, however, sensitive only to sulphathiazole.

Summary

A case is described of pneumonia and septicaemia, fatal within 24 hours. *Achromobacter anitratus* (Schaub and Hauber) Brisou was isolated from the sputum, and a morphologically identical diplococcus was seen in sections of the lung, spleen, and adrenals. Proof that this organism may behave as a pathogen has not previously been established.

We are indebted to the Central Public Health Laboratory, Colindale, for identification of the strain.

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Western Australian Medical School has started a scheme under which fifth-year students will accompany general practitioners on their rounds in Perth to learn more about disorders encountered in family practice but uncommon in hospitals. Thirty students will train under the scheme during the next year.

THE ABSENT TESTICLE

A REPORT ON A SURVEY CARRIED OUT AMONG SCHOOLBOYS IN NOTTINGHAM

BY

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AND

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It is not uncommon to find at routine medical examinations of schoolboys that one or both testicles appear to be absent from the scrotum. This poses the problem of whether the testicle is undescended, maldescended, or retracted—a problem which becomes more serious as the child grows older.

Climatic conditions, the temperament of the child, an active cremasteric reflex, and other factors may prevent the doctor from palpating a retracted testicle. A maldescended testicle may be felt superficially above the inguinal ligament, while a truly undescended testicle cannot be palpated inside or outside the scrotum. In the past, various methods of treatment have been undertaken. Physicians have often given a series of hormone injections in order to hasten sexual development and produce a descent of the testicle; and endeavours have also been made to bring about its descent surgically, the success of this procedure depending on the blood-supply and the length of the spermatic cord. In the opinion of others it is held that treatment is unnecessary until puberty is imminent, the view being taken that the undescended testicle often descends unaided.

It is therefore a matter of some importance to determine, if possible, the natural history of the undescended testicle, and to find out when, if at all, treatment is necessary.

Several surveys have been made in the past in an endeavour to throw light on this problem. Scorer (1955, 1956) examined some 1,500 babies after birth and again after the lapse of a year. He found 3.4% to have undescended testicles. A number of reports (Coley, 1919; McCutcheon, 1938; Smith, 1941) have been made concerning boys above and below 15 years of age. Of these, 3.3 to 9.4% under 15 years and 0.6 to 0.8% over 15 years had undescended testicles. In 1956–7 a survey (Society of Medical Officers of Health, 1958) was made among schoolboys in East Anglia between the ages of 5 and 17 years which gave the following results: 4% of the boys of 5, 8, and 11 years showed unilateral undescended testicles and 2% showed bilateral undescended testicles; the average proportion among school leavers aged 14–17 years was found to be 0.6% undescended on one side and 0.1% on both sides. A marked variation was noted among the findings of the several doctors taking part in the survey. It was difficult to determine by one examination alone whether an apparently undescended testicle was actually undescended or merely retractile.

Present Survey

This survey was conducted during 1957–8 by five medical officers in the schools of the Nottingham Education Committee. At the routine examination of 19,024 boys aged 5, 8, 11, and 14–17 years unilateral and bilateral undescended testicles were noted. The figures are shown in the accompanying Table. It is seen that the total incidence of unilateral and bilateral undescended testicles in 1957 rises from 2.29% at 5 years to 6.23% and 5.42% respectively at 8 and 11 years, falling to 0.41% at 14–17 years. In 1958 there were 1.15% of undescended testicles at 5 years, rising to 2.40% and 4.05% at 8 and 11 years, and falling to 0.23% at 14–17 years. Boys who had received any form of treatment were not included in the figures.

Results of Routine Examination of 19,024 Boys Aged 5, 8, 11, and 14–17 Years

Testicle Absent	5 Years		8 Years		11 Years		14–17 Years	
	No.	%	No.	%	No.	%	No.	%
1957:	(2,174)		(2,166)		(2,304)		(1,716)	
Right	21	0·97	70	3·23	58	2·52	4	0·23
Left	7	0·32	25	1·15	23	1·00	2	0·12
Both	22	1·01	40	1·85	44	1·91	1	0·06
Total	50	2·29	135	6·23	125	5·42	7	0·41
1958:	(2,965)		(2,038)		(2,666)		(2,995)	
Right	13	0·44	24	1·17	51	1·91	4	0·13
Left	7	0·24	12	0·59	18	0·68	3	0·10
Both	14	0·47	13	0·63	39	1·46		
Total	34	1·15	49	2·40	108	4·05	7	0·23

The figures in parentheses represent the yearly numbers in the various age-groups.

Discussion

From the figures it is seen that the right testicle is more frequently undescended than the left, and that bilateral undescended testicles are much less common. There is, however, a very marked reduction in the frequency of undescended testicles, both unilateral and bilateral, in the age-groups of 11 years to 14–17 years, thus giving a total proportion of undescended testicles after puberty of 0.41% in 1957 and 0.23% in 1958. This suggests that at the age of puberty most testicles descend without treatment. It is probable that two factors are concerned in explaining the fluctuation of the figures in the 5, 8, and 11-year groups: firstly, the variation in observers, and, secondly, the possibility that retraction may occur more readily in boys of 7–11 years than in 5-year-olds.

It is difficult to explain why the figures should be lower in 1958 than in 1957. Perhaps the experience gained by the observers in the earlier year may have been a factor in the more successful palpation of some retractile testicles.

Summary

A survey of 19,024 boys at the ages of 5, 8, 11, and 14–17 years was made in 1957 and 1958 to determine the number of unilateral and bilateral undescended testicles.

A marked fall in the percentage of these conditions was found to occur between 11 years and 14–17 years.

It is suggested that hitherto undescended testicles may naturally descend into the scrotum at puberty. If this is true it may produce a reorientation in the approach to treatment.

We thank Dr. R. G. Sprenger, principal school medical officer, who instigated and encouraged us in this investigation, and our colleagues of the School Health Service, Nottingham, for their help in this survey. We also thank

Dr. Sumner, of the department of education, University of Nottingham, for his kind assistance in the preparation of the statistical evidence.

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A POTENTIAL NEW THERAPY FOR FEBRILE SEIZURES*

PRELIMINARY REPORT ON DEVELOPMENT OF *N*-PHENYLBARBITONE

BY

J. GORDON MILLICHAP,† M.D., M.R.C.P., D.C.H.

Febrile seizures occur commonly in infants and young children, and generally in response to fever caused by acute infections of the upper respiratory tract. The height of the fever is an important factor in aetiology, and the body temperature at the onset of the convulsion is a reliable measure of the febrile-seizure threshold (Millichap, 1959). Patients with a high threshold convulse only in response to fever of 41° C. (105.8° F.) or above, whereas those who are most susceptible have seizures with fever of 38.5° C. (101.3° F.) or below.

Conventional methods of treatment have been found inadequate. Phenobarbitone, administered intermittently at the time of febrile episodes and in combination with acetylsalicylic acid or continuously in repeated daily doses, failed to prevent recurrence of febrile seizures in 48% of 40 patients treated; phenytoin sodium given regularly and daily was entirely ineffective in seven patients. Tepid water-baths and other methods of hydrotherapy also were unsatisfactory (Millichap, Aledort, and Madsen, 1960).

The ideal therapy for febrile seizures should have both antipyretic and anticonvulsant effects in doses relatively non-toxic. Since seizures occur only at the time of an acute febrile illness, the action of the drug should be rapid in onset and allow intermittent administration so that necessity for continuous medication may be avoided. In the present study a new compound with potential activity against fever-induced seizures has been developed as the result of laboratory tests in animals. Its clinical efficacy has been demonstrated in preliminary trials.

Methods

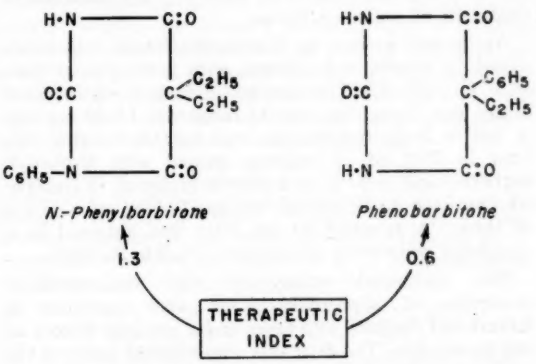
Febrile seizures were induced in young Swiss albino mice by means of a microwave diathermy generator, according to a method described previously (Millichap, 1959). Drugs were tested for their ability (1) to retard the rate of rise of body temperature, (2) to raise the threshold convulsive temperature (temperature at the onset of clonus), and (3) to abolish the seizure. Various doses were employed and between 5 and 10 mice were treated at each dose level. Responses of test animals were compared with those of controls. The effects of acetylsalicylic acid, phenobarbitone, and phenytoin sodium were examined initially so that the efficacy of new drugs could be compared with conventional methods of treatment and their potential clinical value assessed. The selection of new chemicals for testing was facilitated by preliminary observations of the activity of various classes of pharmacological agents against seizures induced experimentally (Millichap, 1958).

Results

Acetylsalicylic acid in oral doses of 10, 50, and 100 mg./kg. failed to retard the rate of temperature rise in mice and in toxic doses (600 mg./kg.) increased the severity of the febrile seizure. The inadequacy of acetylsalicylic acid in the prevention of febrile seizures may be explained in part by the failure of its antipyretic effect in the presence of a rising temperature. The ineffectiveness of phenytoin sodium against fever-induced seizures in children was observed also in animals; oral doses of 10, 20, and 50 mg./kg. exacerbated the clonic pattern. Phenobarbitone retarded the rate of rise in body temperature and prevented the febrile seizure, but large depressant doses were required; with smaller doses protection from seizures was incomplete but the threshold convulsive temperature was elevated.

Of 60 new chemicals tested, *N*-phenylbarbitone ("pyrictal") was the most potent anticonvulsant; its action was rapid in onset and toxicity was relatively low. In doses larger than those necessary for control of seizures in mice, hyperexcitability was the principal side-effect and, in contrast to phenobarbitone, sedation was of minimal degree; tremor and clonic movements were observed with sublethal doses of 600 mg./kg. Similar side-effects have been noted in other species, in acute and chronic toxicity studies performed by the Wellcome Research Laboratories, U.S.A. (E. J. deBeer, personal communication).

The chemical structure of *N*-phenylbarbitone and of phenobarbitone and the respective therapeutic indices are as follows:



The therapeutic index is a measure of the margin of safety and potential usefulness of a drug; it is obtained by dividing the dose which causes minimal signs of toxicity in 50% of animals (TD_{50}) by that which protects 50% of animals from the experimental seizure (ED_{50}).

Laboratory and clinical evaluations of *N*-phenylbarbitone and phenobarbitone are compared in the Table. Determinations of parallelism and estimates of relative potency and toxicity were made by the methods of Litchfield and Wilcoxon (1949). Dose-effect lines of the two drugs were parallel. The potency of anticonvulsant

*Presented at the Ninth International Congress of Paediatrics, Montreal, Canada, July, 1959.

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effect was not significantly different (potency ratio (1.45) $<f_{p.r.}$ (1.82)), but the neurotoxicity of phenobarbitone was three times that of *N*-phenylbarbitone (toxicity ratio: 3.1, with 95% confidence limits of 5.3 to 1.8).

Laboratory and Clinical Evaluation of N-Phenylbarbitone Compared with Phenobarbitone

Evaluation	*N*-Phenylbarbitone	Phenobarbitone
Laboratory:		
Anticonvulsant ED_{50}	150 mg./kg. (112–200)*	103 mg./kg. (61–173)
Neurotoxic TD_{50}	190 mg./kg. (152–238)	61 mg./kg. (37–100)
Antipyretic activity ..	18%	1·6%
Test rate of rise ..	5·0±0·27° F./min.†	6·59° F./min.
Control rate of rise	6·1±0·35° F./min.	6·70° F./min.
t, df, P	2·43, 12, <0·05	—
Time of maximal effect	1½ hours	3 hours
Clinical:		
Febrile seizure control	100% (12)‡	52% (40)‡

* 95% confidence limits.
† Mean ± standard error.
‡ Difference significant: $\chi^2=6·7$, $P<0·01$. No. of patients shown in parentheses.

Antipyretic effects were expressed as the percentage retardation of rate of rise of body temperature. The effect of *N*-phenylbarbitone was significant in non-toxic doses (150 mg./kg.), whereas phenobarbitone was inactive at a toxic dose level (50 mg./kg.). In contrast to *N*-phenylbarbitone, the antipyretic effect of phenobarbitone was irregular and a satisfactory dose-response curve was not obtained.

Clinical Evaluation

Anticonvulsant activity of *N*-phenylbarbitone was evaluated in 20 institutionalized patients with major, minor, or combined seizures previously uncontrolled by conventional anti-epileptic drugs. The average daily dose administered orally was 17 mg./kg. A reduction in the incidence of seizures of 75% or more was obtained in 8 out of 15 patients with major seizures and in 9 out of 10 patients whose seizures were minor in type. Myoclonic, opisthotonic, and absence seizures were controlled more effectively than the tonic or tonic-clonic pattern, and a combination of phenytoin sodium and *N*-phenylbarbitone was necessary for satisfactory treatment of major epilepsies.

Antipyretic activity of *N*-phenylbarbitone was determined in infants and children with fever greater than 38.3° C. (101° F.). The average single dose administered orally was 23 mg./kg. and the range was 14–30 mg./kg. A fall in body temperature was recorded within one hour in 75% of 71 children treated with *N*-phenylbarbitone and in 31% of a control group of 16 children who received no antipyretic therapy for the same period of time. A response to the drug was obtained in a significant proportion of patients ($\chi^2=9.0$, $P<0.01$).

The combined antipyretic and anticonvulsant properties of *N*-phenylbarbitone were examined in infants and children with fever and a previous history of febrile seizures. The drug was administered orally at the onset of acute infection in doses of 20 mg./kg. Febrile seizures did not occur in 12 patients treated with *N*-phenylbarbitone, whereas the incidence of recurrence was 48% in 40 patients who received phenobarbitone.

In febrile children treated intermittently no side-effects were observed. Of epileptic patients who received the drug continuously, one was restless, one was anorexic, and one was sedated. Drowsiness was increased transiently in four patients who were treated with *N*-phenylbarbitone in addition to phenobarbitone and phenytoin sodium.

Summary and Comment

The ideal therapy for the prevention of febrile seizures is an anticonvulsant which acts also as an antipyretic and inhibits heat production during the initial and pyrogenic stage of a febrile illness. It should elevate the febrile seizure threshold and prevent a rise in body temperature above the threshold convulsive temperature for the individual patient.

Conventional methods of treatment have been found inadequate. Acetylsalicylic acid facilitates heat loss in a febrile patient but has no effect on heat production; the optimum antipyretic effect is obtained when the administration of the drug coincides with the expected defervescence of the fever (Goodman and Gilman, 1955). Phenobarbitone is relatively ineffective as an anticonvulsant in the febrile patient.

N-phenylbarbitone has been developed as a specific therapy for febrile seizures. The efficacy has been demonstrated in laboratory and clinical tests.

In contrast to acetylsalicylic acid, *N*-phenylbarbitone retards the rise of body temperature during the induction of fever in animals, and compared with phenobarbitone it is equally effective in the prevention of experimental febrile seizures, has only one-third the toxicity, and is antipyretic in non-depressant doses. In epileptic patients, clonic, opisthotonic, and absence seizures are responsive, but the major tonic pattern is not well controlled.

To be accepted for general use, the new compound must prove superior in efficacy and less toxic than the therapy employed at present. The results of initial trials of *N*-phenylbarbitone in children with fever and seizures are encouraging and further evaluation of its clinical efficacy against febrile seizures, hyperpyrexia, and minor epilepsies seems warranted.

N-phenylbarbitone (pyrictal) and other new chemicals were synthesized and supplied by Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N.Y. The drug was developed at the Departments of Paediatrics and Pharmacology, Albert Einstein College of Medicine, and the Bronx Municipal Hospital Center, New York City. I am indebted to Dr. Bernard I. Kramer for his supervision of the trials of the drug in patients with fever and febrile seizures, to Dr. Richard C. Cooke and Dr. Philip R. Dodge for permission to conduct trials at the Myles Standish State School, Taunton, Mass., and to Dr. Alfred Gilman for his interest and encouragement.

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The Soviet journal of medical abstracts, *Soviet Medical Literature*, will almost double the number of its references in 1960, and will appear in ten series instead of four: internal diseases, endocrinology, balneology and physiotherapy, venereal disease; tuberculosis; infectious diseases, epidemiology and parasitology, microbiology and antibiotics; surgery, traumatology and orthopaedics, urology; paediatrics; oncology, roentgenology, radiology; hygiene and sanitation, history of medicine, forensic medicine; otorhinolaryngology, ophthalmology, stomatology; neuropathology and psychiatry; and obstetrics and gynaecology. (Unesco: *M. Bull.* "1960.02.").

Medical Memoranda

Chewing-gum in the Bronchi

The aspiration of foreign bodies into the air passages is an accident which may happen to subjects of all age-groups. Numerous reports in the literature describe a large variety of inhaled objects. Indeed, any object that is held in the mouth may at some time be inhaled, provided it is of a size to allow passage through the larynx.

In the words of Jackson and Jackson (1934), "It is the duty of everyone to spread the propaganda of prophylaxis against accidents of any kind." The purpose of this report is to point out that the now widespread use of chewing-gum is apt to be attended by fatal consequences, and that some care is necessary for the safe indulgence even of this simple habit. Despite the prevalence of the habit both in this country and in the United States we are not aware of any similar case which has been reported. Jackson (1919) and Jackson and Jackson (1934) make no mention of chewing-gum as a foreign body.

CASE REPORTS

Case 1.—A man aged 62, enjoying reasonable health, was found dead in his garden by his wife, who was taking him tea at 5 p.m. on November 22, 1952. He had had nothing to eat since lunch, and had not obviously been strenuously employed. Necropsy was performed after 42 hours, and the main findings were as follows. Lividity was limited to the dorsal part of the body and the ears. The heart weighed 410 g. and showed left ventricular hypertrophy, with no evidence of old or recent infarction. Both coronary arteries showed advanced calcified atheroma but without occlusion. There was no pulmonary embolus. The lungs were fixed by old adhesions to the chest wall and showed moderate emphysema. The trachea and bronchi showed reddening of the mucosa, and occluding the right main bronchus was a single lump of chewing-gum (see Fig. 1 a). There was no suppuration.

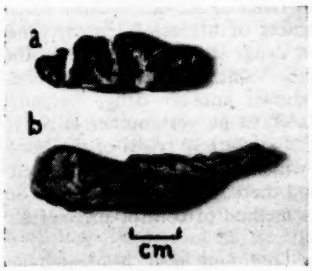

FIG. 1

Case 2.—A man, also aged 62, employed by an engineering firm, was apparently in good health. During the morning break he had been chatting with other men, and afterwards when walking towards his machine he was seen to fall suddenly. He was dead when medical aid arrived. Necropsy was performed within 48 hours, and the main findings were as follows. The heart weighed 300 g. and showed fine scarring of the myocardium. The coronary arteries showed severe calcifying atheroma but there was no thrombosis. The left main bronchus contained an elongated and flattened mass of chewing-gum (see Fig. 1 b). The main bronchus was not totally occluded, and the mucosa was inflamed; a little mucopus was present. The lungs were congested but showed no evidence of infection or collapse.

COMMENT

In Case 1 there was evidence of diminished cardio-respiratory reserve, and in the absence of definite signs of asphyxia death was attributed to vagal inhibition resulting from sudden impaction of the foreign body in the bronchus.

In Case 2 there was evidence of diminished cardiac reserve. The purulent bronchitis was thought to indicate that the chewing-gum had been inhaled some time before death, and that death was due to coronary insufficiency and bronchospasm.

It seemed that the difference in the shape of the two specimens in these cases might well be related to the difference in the degree of obstruction. Furthermore, in Case 2 the foreign body was composed of two portions lightly adherent to one another, and it seemed likely that more than one piece of chewing-gum had been inhaled. Such an event is indeed possible, for those who indulge this habit feel the need of adding a fresh piece as soon as the flavour of the old one has been lost. To satisfy ourselves on this point we obtained three common varieties of chewing-gum; these were dried and weighed individually after all the soluble matter had been removed by thorough mastication. The appearance and weights of these varieties together with the weights of the two specimens were:

	Colour	Weight
Spearmint	Grey	0.79 g.
Wrigley P.K.	,, ...	0.38 g.
Rowntree "beech nut"	Brown	0.45 g.
Case 1	,, ...	1.35 g.
Case 2	Grey-green	1.36 g.

From these findings we conclude that the specimen from Case 1 is composed of three beech-nut chewing-gums. The specimen from Case 2 does not appear to be of the same composition, but almost certainly represents several chewing-gums in one lump.

Any object temporarily held in the mouth may be inhaled. The longer it remains in the mouth the greater will be the chance of accidental aspiration, and chewing-gum is usually held in the mouth very much longer than sweets that dissolve. Perhaps on this account chewing-gum is more often taken by people who are engaged upon some physical activity. This association with work is an additional danger, for if involuntary gasping occurs during activity the chance of aspiration is greatly increased. Finally, the habit of adding one gum to another in order to maintain the flavour must be condemned. If gum must be chewed it is better to chew one at a time and thus avoid forming a large plug which is capable of obstructing a main bronchus.

We acknowledge with thanks the encouragement of Professor J. M. Webster and the kindness of Mr. D. H. B. Harfield, Hampshire County Coroner, and Mr. Frank Cooper, Coroner for S.E. Staffordshire, for allowing us to report the cases. We also thank Mr. D. E. D. Kimpton, of the Manor Hospital, Walsall, for the photograph.

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Road deaths throughout New Zealand in 1959 totalled 349, a reduction of 30, or 8% on the 1958 figure. The rate per 10,000 vehicles was the lowest for the past 30 years, excluding 1945. According to a report by the Municipal Association's representative on the National Roads Board, Mr. G. A. HARRIS, the number of road vehicles in New Zealand by 1970 may reach 1.1 million, one to every 2.5 people, and an increase of 78% on the 1958 figure.

Reviews

AN EVOLUTIONARY APPROACH TO IMMUNITY

The Clonal Selection Theory of Acquired Immunity. By Sir Macfarlane Burnet, O.M., F.R.S. (Pp. 209+ix. 22s. 6d.) London: Cambridge University Press. 1959.

"The clonal selection theory of antibody production is based on the concept that the antibody-producing cells of the body form part of a mobile population of mesenchymal cells constantly undergoing physiological and mutational change. When mutational change occurs a new clone is initiated. It is postulated that mesenchymal cells carry surface sites analogous to the specific patterns on the antibody patterns they produce. Stimulation by contact of these sites with the corresponding antigenic determinant may provoke more than one type of response, but the crucial one is the proliferative response which allows a selective advantage to the clone concerned. The theory differs from the standard interpretation of antibody production in replacing the concept that in one way or another the antigen actively enforces production of a new pattern of specific globulin, by the view that somatic mutation and selection within the mesenchymal cell population can have the same overall effect."

This is the author's own summary of the clonal selection theory as elaborated in the first chapters of this book, where arguments are advanced against the rival claims of Erhlich's side-chain theory, the Haurowitz–Pauling direct template theory, the Burnet–Fenner indirect template theory, and Jerne's natural selection theory. To the two fundamental, but experimentally unproved, postulates (*a*) that mesenchymal cells, chiefly the lymphocytes, have in embryonic life undergone somatic mutations resulting in the development of clones of cells with differing surface patterns of sufficient variety to provide sites with a "close enough" fit to all antigenic determinants to allow some reaction, and (*b*) that contact with the appropriate antigen leads to selective proliferation of the clone, and consequent increased production of its antibody globulins—there must be added a third concept, also based on "circumstantial" evidence, (*c*) that there exists a homoeostatic mechanism which ensures that "forbidden" clones (i.e., clones which might react with "self" antigens) are destroyed instead of being stimulated.

The subsequent chapters are devoted to the examination, in the light of this theory, of phenomena such as, to name but a few, immunological tolerance, pathological conditions attributable to immune response (e.g., Hashimoto's disease), modifications of the course of infectious disease as a result of anomalies of the immune response, proliferative diseases of the reticular tissue and mesenchymal cells, and neoplastic disease. All are discussed with great erudition, and, with much ingenuity and further *ad hoc* assumptions where necessary, are shown to be capable of explanation in terms of somatic mutation and clonal selection.

The author claims that this approach to the problems of immunity, embodying the basic concept of mutation and selective survival, is essentially an evolutionary one, in keeping with the Darwinian hypothesis. The reader may nevertheless feel that, however neatly the theory can be adapted to explain the many conundrums of immunology, it would be more convincing if experimental evidence could be produced to substantiate the assumptions on which it is based.

J. S. K. BOYD.

AUTHORITATIVE BOOK ON LEPROSY

Leprosy in Theory and Practice. Edited by R. G. Cochrane, M.D., Ch.B.(Glas.), F.R.C.P.(Lond.), D.T.M.&H. Foreword by Sir George McRobert, C.I.E., M.D.(Aberd.), F.R.C.P. (Lond.). (Pp. 407+xv; illustrated. 84s.) Bristol: John Wright and Sons Ltd. 1959.

Though it is one of the oldest recognized diseases of man, a full understanding of leprosy is yet lacking. This is, in part, because the causative organism is peculiar to man; it has successfully been maintained neither in animals nor in culture. Also the disease varies greatly in its manifestations, not only from one place to another, but in different individuals in the same place. It is hardly surprising that the considerable literature on it is conflicting and confusing. This book presents a timely, balanced appraisal of accepted fact and of modern views on leprosy in all its aspects. In his task of editorship Dr. R. G. Cochrane, himself an acknowledged authority on the disease with practical experience of it in all parts of the world, has been assisted by some two dozen contributors, some not leprologists but each an expert within the field of his own contribution. There are authoritative sections on the distribution and epidemiology, pathology, clinical picture and diagnosis, complications, and chemotherapy of the disease. In addition there are other interesting and very valuable chapters, perhaps particularly those by Mr. P. W. Brand on the orthopaedic relief of the deformities which are such distressing features of neglected leprosy, and Dr. T. F. Davey on new drugs showing promise in the treatment of the disease. Since then the latter contributor has, in fact, shown another drug, "etisul" (diethyl dithiol*iso*phthalate), to be yet another effective chemotherapeutic agent. The last 30 pages of the book contain appendices in which various laboratory techniques are described; and there, also, is information on plastic surgery, and on a method of control successfully applied in a limited area.

The volume, well printed and well illustrated, is presented in attractive form by the publishers. Though the price is high, it is not unduly so by modern standards. This work will be found to be the best and most modern on its subject; it will constantly be consulted by those dealing with the disease, and equally by those who wish to further knowledge on various aspects of it.

A. R. D. ADAMS.

THE MEDICAL MUSEUM

Medical Museum Technology. By J. J. Edwards and M. J. Edwards. (Pp. 172+ix; illustrated. 21s.) London: Oxford University Press. 1959.

The book is divided into three roughly equal parts. The first gives a fascinating, though brief, account of the development of early methods of preserving specimens and the organization of museums from the fifteenth century to the present day. The second describes proved methods of preservation and display acquired by the authors during many years' experience, and reviews newer methods of injection and embedding which still await the verdict of time. The third discusses the design, organization, and staffing of a modern medical museum. Inevitably the treatment is selective, but one misses a reference to the pioneer work of Sidney Daukes

on visual teaching, which was so widely followed during the period between the wars. Since this is not a mere catalogue of methods, it seems a pity that the technical section was not also treated on historical lines. Past mistakes and enthusiasms often give an insight into present difficulties, especially in an empirical subject such as this. The impression is given of a *cri de cœur* from one who has mastered the art in all its intricacies, knows the part a museum still has to play in medical education, and is not impressed by glossy superficial montages of the contemporary exhibition type.

The great medical museums probably reached their zenith in the second decade of this century, when morbid anatomy was a prime concern of heads of teaching departments and of the leaders in medicine and surgery. To-day the focus of attention has moved to other rapidly extending fields of inquiry and the museum has tended to become a nostalgic tradition. The young technician is quick to realize that such patiently acquired skills no longer attract the attention they merited in the past, and the trained preparator is becoming extinct in consequence. It is to be hoped that this book will revive interest in medical museums and help them to meet the challenge of the times.

L. W. PROGER.

TEXTBOOK OF NEUROLOGY

A Textbook of Neurology. By H. Houston Merritt, M.D. Second edition. (Pp. 765; illustrated. 93s. 6d.) London: Henry Kimpton. 1959.

This excellent new textbook has reached its second edition in four years. It is factually accurate and inclusive, and yet concise, each brief nosological section having three or four well-chosen references at its foot. Its orientation is that of the bedside physician, its basis that of neuropathology. The book bridges the gap between the ponderous Germanic texts of a few years ago and the more enlightened and encouraging books given to the student to-day, which lack the detail needed by the established physician for day-to-day reference. It is lucid, well indexed, and practical, both the recognition of the disease and its treatment being adequately discussed. Lastly, for an American text it is surprisingly cheap, which is probably a reflection of its wide sale.

DENIS WILLIAMS.

CONTROLLING FERTILITY

Modern Science and the Human Fertility Problem. By Richard L. Meier. (Pp. 263+xiii. 48s.) New York: John Wiley and Sons. London: Chapman and Hall. 1959.

Dr. Meier has trained in organic chemistry, social science, and economics, and brings all these disciplines to bear in this book, which, like so many others, is concerned with the need to stabilize world population in order to secure the proper economic development of the poorer territories. He illustrates the problem by reference to certain underdeveloped though densely populated countries, and discusses the various methods which offer some hope of limiting human reproduction by orally administered chemicals. The latter include those which aim to depress the pituitary or the gonads in either sex, and those which act by damaging the fertilized ovum or by killing the products of conception *in utero*. The author sees hope in the more recent developments which have resulted in the introduction of the 19-nor-steroids, which, in the Puerto Rican experiment, proved effective in lowering fertility, and anticipates that a reliable and non-injurious oral contraceptive will probably become available for mass manufacture by 1980. He is not deterred by possible religious and ethical difficulties, and envisages that the inevitable improvements in methods of communication during the next 20 years will ensure that the product is widely distributed and used. Even so, Dr. Meier is not convinced that an efficient oral contraceptive alone will be enough to keep the world population low enough to prevent starvation; he considers that a certain amount of voluntary surgical sterilization will also be necessary. This book, if rather repetitive in parts, contains many interesting points which should be of value to those concerned with the broad picture of human fertility.

T. N. A. JEFFCOATE.

CHILDREN'S SLEEP

Le Sommeil de l'Enfant avant Trois Ans. By Robert Debré and Alice Doumic. Preface by Professor Georges Heuyer. (Pp. 195+xii; illustrated. 800 fr.) Paris: Presses Universitaires de France. 1959.

In this little book on children's sleep Professor Debré and Dr. Doumic deal with the physiology and pathology of sleep in children up to 3 years of age. They consider that sleep is an active and co-ordinated process of inhibition of all bodily functions, and they analyse these functions separately during the process of going to sleep, in the middle of sleep, and on awakening. They devote much space to the normal electroencephalographic patterns, which change so rapidly during the first three years, and illustrate their thesis by several tracings. They point out that the greatest difference between the E.E.G. patterns of adults, bigger children, and infants is noticeable on going to sleep and on awakening, and believe that this may account for the frequent clinical disturbances which occur in small children during these times.

The authors correlate the development of the sleep pattern of individual children with their development in the motor and intellectual spheres, and in the field of character. Disturbances of sleep are analysed on the basis of a personal study of 75 children; several full case histories are given. The authors find that sleep disturbances are least common between 3 and 9 months of age, and most common from then to 3 years. The causes vary from hunger to physical illness, night terrors, and insecurity. Treatment of the disorders is based on accurate diagnosis. More space is—correctly—devoted to the prevention of behaviour problems than to their treatment, and to the best methods of re-establishing a normal physical and psychological background. Drug treatment and psychotherapy play little part, and in my opinion psychotherapy for small children, as described, is likely to be of little value. This is the only adverse comment on a lively little book.

JOHN LORBER.

EXAMINING THE PATIENT

Physical Diagnosis. The History and Examination of the Patient. By John A. Prior, M.D., Jack S. Silberstein, M.D., and contributors. (Pp. 388; illustrated. 56s.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

This book is a product of the Ohio State University College of Medicine. The authors in writing this textbook have had the assistance of eight of their specialist colleagues. It has many merits: it is well produced on excellent paper and has many good photographs; it emphasizes the importance of good history-taking and

careful examination ; its approach is traditional, and its teaching is designed to give the medical student a sound foundation on which to build his clinical practice ; some of the sections written by the specialists are exceptionally well done. Yet a textbook of this nature must be judged by its well-established rivals, and by this standard this book does not succeed. There is at least one standard English work in this field which is immeasurably more useful to the student. Any book which sets out to teach physical diagnosis will do this more successfully in its tenth edition than in its first. Omissions and errors will by then be corrected, and the book will be polished to perfection by the comments of a succession of readers.

This book, in some sections at least, lacks the critical approach to symptoms and signs which the modern education of the medical student demands. It is authoritarian where it might well be sceptical, and it does not always assess the value of the signs described. For example, the signs of advanced emphysema are detailed without any indication that a diagnosis should be made before these gross signs appear. Omissions are many: there is no instruction for recording the position of the apex beat, no description of the "opening snap," no advice on distinguishing the enlarged left kidney from an enlarged spleen, no good description of the several components of clubbing, and, above all, no indication that "observer error" exists. Mistakes are few, but it is extraordinary that Harrison's "grove" should be attributed to rickets without mention of respiratory obstruction. There is, too, an occasional naivety in the book, such as the remark that the "eyes are the windows of the soul." This is not yet a good textbook, but it is good enough to deserve another edition.

D. V. HUBBLE.

Cosmetic Science is the report of a congress organized by the Society of Cosmetic Chemists of Great Britain which was held in London in April last year. It is made up of sixteen original papers; each paper is followed by a discussion which adds interest to the subject, and all of these appear to be very well reported. Many of the papers are of interest almost exclusively to the cosmetics industry, dealing for example with manufacturing methods and problems. Dr. E. J. Moynahan contributes a paper on patch testing, Dr. F. J. Ebling on the biology of the skin, and Dr. J. G. Feinberg on allergy. These three excellent papers are written primarily for the scientific non-medical reader. The whole tone of this book indicates an industry with a sense of responsibility which is anxious to progress with advances in the biological, physical, and medical sciences. (Butterworths Scientific Publications; pp. 327 + xv; illustrated; 60s.)

A physician, a surgeon, and a gynaecologist have collaborated with a distinguished authority on antibiotics in producing *Antibiotic and Sulphonamide Treatment*, edited by M. E. Florey (Oxford University Press, 1959, 10s. 6d.). It is described as being a "Short Guide for Practitioners" and a strictly practical pocket manual of 150 pages. Commended in a foreword by Lord Evans, it consists first of accounts of the properties of the drugs concerned and then of instructions for their use in specific infections, which are dealt with in alphabetical order from "Actinomycosis" to "Yaws" and in diseases of systems. Within such covers there is no room for discussing interesting controversial matters: the authors have had to be terse and dogmatic, but they offer much sound advice. The inclusion of the sulphonamides, which are accorded a considerable place in present-day therapy, adds to the practical usefulness of the book.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Metabolic Homeostasis. A Syllabus for Those Concerned with the Care of Patients. By Nathan B. Talbot, M.D., Robert H. Richie, M.D., John D. Crawford, M.D., and Edith S. Tagrin. (Pp. 132+xii ; illustrated. 24s.) Cambridge, Mass.: Harvard University Press (Commonwealth Fund). London: Oxford University Press. 1959.

L'Électrocardiogramme Dysmétabolique. Perturbations Ioniques et Électrocardiogramme. By A. Larcan and C. Huriet. (Pp. 222 ; illustrated. Fr. 2,500.) Paris: Masson et Cie. 1959.

The Prevention of Incurable Disease. By M. Bircher-Benner, M.D. (Pp. 125+xiv ; illustrated. 7s. 6d.) London: James Clarke and Co., Ltd. 1959.

Gestation. Transactions of the Fifth Conference, March 11-13, 1958, Princeton, N.J. Edited by Claude A. Villee, Ph.D. (Pp. 262 ; illustrated. $5.75.) New York: Josiah Macy, jun. Foundation. 1959.

Gynecological Therapy. By Josef Novak, M.D. (Pp. 258+xi; illustrated. 66s.) New York, London, Toronto: Blakiston Division, McGraw-Hill Book Company. 1960.

Principles for British Agricultural Policy. A Study Sponsored by the Nuffield Foundation. Edited by H. T. Williams, B.A. (Econ.). (Pp. 317+xiii; illustrated. 18s.) London, New York, Toronto: Oxford University Press, for the Nuffield Foundation. 1960.

Metals and Engineering in Bone and Joint Surgery. By Charles Orville Bechtol, M.D., Albert Barnett Ferguson, jun., M.D., and Patrick Gowans Laing, M.B., B.S., F.R.C.S. (Pp. 186+vii; illustrated. 64s.) London: Baillière, Tindall and Cox, Ltd. 1959.

Pediatric Pathology. By Daniel Stowens, M.D. (Pp. 676+xiii; illustrated. £8.) London: Ballière, Tindall and Cox, Ltd. 1959.

The Surgical Treatment of Facial Injuries. By Varaztad Hovhannes Kazanjian, M.D., D.M.D., and John Marquis Converse, M.D. Second edition. (Pp. 1,110+ix; illustrated. £12 16s.) London: Baillière, Tindall and Cox, Ltd. 1959.

Cinefluorography. Proceedings of First Annual Symposium on Cinefluorography, Sponsored by the Department of Radiology, University of Rochester, New York, November 14 and 15, 1958. Edited by George H. S. Ramsey, M.D., James S. Watson, jun., M.D., Theodore A. Tristan, M.D., Sydney Weinberg, and William S. Cornwell, M.A. (Pp. 266+xvi; illustrated. 94s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Prosthetic Principles: Above Knee Amputations. By Miles H. Anderson, Ed.D., John J. Bray, C.P., C.O., and Charles A. Hennessy, C.P., C.O. Edited by Raymond E. Sollars. (Pp. 331 +xi; illustrated. 80s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Biochemical Response to Injury. A Symposium Organized by C.I.O.M.S. Edited by H. B. Stoner, with the assistance of C. J. Threlfall. (Pp. 467+xi; illustrated. 57s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

An Introduction to Gynecological Exfoliative Cytology. A Manual for Cytotechnicians. By Winifred Liu, M.Sc., M.D. (Pp. 127+xi; illustrated. 48s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Shapes of Sanity. A Study in the Therapeutic Use of Modelling in the Waking and Hypnotic State. By Ainslie Meares, M.D., B.Agr.Sc., D.P.M. (Pp. 468+xii; illustrated. £5 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Pathology of the Heart. By S. E. Gould, M.D., D.Sc. Second edition. (Pp. 1,138+xvi; illustrated. £13.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Diagnosis and Treatment of Tumors of the Chest. Sponsored by the American College of Chest Physicians. Editor-in-Chief: David M. Spain, M.D. (Pp. 371+xii; illustrated. $14.75.) New York and London: Grune and Stratton. 1960.

Les Manipulations Vertébrales. By Robert Maigne. (Pp. 246; illustrated. NF. 28.) Paris: Expansion Scientifique Française. 1960.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY APRIL 9 1960

STRONTIUM-90 IN HUMAN BONE

The Atomic Energy Authority reports at six-monthly intervals the results of radiochemical assay of human bones for strontium-90. The latest of these reports just published[1] gives the results of some threescore samples received in the earlier part of 1959. The delay is not due, as some reports have suggested, to declassification of "secret" results; on the contrary the work is unclassified. In fact any reputable analyst of appropriate experience could do an assay for about £50: that is the cost of the skilled staff and the specialist equipment. The delay is related partly to this need to use skilled analysts, and partly due to the nature of the assay, which requires the lapse of some months for samples of very low activity, to confirm that only strontium-90 and not strontium-89+90 is being measured.

The recent analyses show, as could have been predicted, that human bone was more contaminated with strontium-90 in 1959 than in previous years. What could not be accurately forecast was the exact levels. The bone contaminated is the recently accreted bone, which derives its salts from plasma, which in turn derives its calcium and strontium largely from the current diet of the individual; and diet is a somewhat variable affair. In a primitive community living off their own land, the inhabitants' bone would reflect the local contamination. But in Great Britain to-day food is largely derived from stores—grain from overseas, canned and frozen vegetables, imported cheese, and chilled meat. Milk, however, is mostly freshly produced, though often transferred over long distances within the country.

The Agricultural Research Council is now keeping watch on the contamination of our diet by strontium-90.[2 3] It appears that the average man derived in 1958 rather more than half his strontium-90 from milk and less from other and vegetable sources. Thus the individual is concerned not only perhaps with his local fall-out and local cow, but with fall-out in other areas of the Kingdom and abroad, not only with the recent fall-out but that of a year or more ago. Fortunately most of the dairy land is in the drier and more fertile parts of the country, but the A.R.C. also keeps watch on isolated wet areas of poor hill pasture.

We know from other reports of the Atomic Energy Authority[4] that fall-out of strontium-90 from mid-1958 to mid-1959 was at about treble the rate before that. Thus, as the level of strontium-90 in fresh milk reflects within a month or so the recent fall-out rather than the total accumulated fall-out, the worst that was likely was a trebling in the value of strontium-90 in recently accreted bone—for example, the skeletons of stillbirths and children up to about a year old. In fact the results of J. W. Arden and colleagues[1] indicate at most a doubling of the values for 1-year-olds to an average of 3 $\mu\mu$c/g. Ca (giving a radiation dose of about 7.5 mrad per year); stillbirths, since they derive their bone from a more varied maternal diet, showed a smaller increase.

Current data indicate that fall-out has declined notably since mid-1959, so that contamination of fresh milk should be declining appreciably. It will take time, however, for the stored foods of 1958–9 to be consumed, but after an interval of a year or so the levels of strontium-90 in them too should reflect the cessation of megaton weapon tests.

In general the situation seems more satisfactory than was at one time expected. Stratospheric debris, it appears, deposits with a half-time of some months to a year or more, the period depending on the latitude and height at which the material is released, rather than 5–10 years as was once thought probable.[5]

With this prospect in view the Medical Research Council[6] stated that, "in the light of knowledge at present available, we should feel that immediate consideration were required if the concentration in human bones showed signs of rising greatly beyond one-hundredth of that corresponding to the maximum permissible occupational level"—that is, above 10 $\mu\mu$c/g. Ca. This widely misquoted and misunderstood statement may now be regarded as unduly pessimistic. Since the stratospheric reservoir is much smaller than then estimated, there is little likelihood that the so-called limit of permissible burden of 100 $\mu\mu$c strontium-90 per gramme of calcium will be reached unexpectedly.

[1] Arden, J. W., Bryant, F. J., Henderson, E. H., Lloyd, G. D., and Morton, A. G., A.E.R.E. R. 3246, 1960, H.M.S.O.
[2] Agricultural Research Council Radiobiological Laboratory, Report No. 1, 1959, H.M.S.O.
[3] Ibid., Report No. 2, 1960, H.M.S.O.
[4] Crooks, R. N., Osmond, R. G. D., Owers, M. J., and Fisher, E. M. R., A.E.R.E. R. 3094, 1960, H.M.S.O.
[5] *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*, 1958, United Nations, New York.
[6] Medical Research Council, *The Hazards to Man of Nuclear and Allied Radiations*, Cmd. 9780, 1956, H.M.S.O.

THE UNDESCENDED TESTICLE

The testes of many mammals are so vulnerable owing to their scrotal position that this feature of male anatomy is rather puzzling. It is commonly claimed that the testes have come to lie in a scrotum so that they may be kept cool, but the temperature range for their maximal activity is surely an adaptation to their scrotal position rather than the reason for it: the elephant, the rabbit-like hyrax, and the whale with their protected abdominal testes are no less fertile than man with all his vulnerability. If the testes do not lie in the scrotum in man or those other mammals normally having scrotal testes, then production of sperm is grossly impaired. If the ram's scrotum[1] is wrapped in wool or the temperature of the testes otherwise raised, the animal loses its fertility; this work has been repeated in man.[2]

The testes develop in the abdomen in man as in all other vertebrates, but at about the seventh month of intrauterine life (or about the comparable time of development in most other mammals) they descend into the scrotum, and remain there except for temporary excursions to the inguinal region caused by contraction of the cremaster muscle. The gubernaculum testis, long held to be associated with testicular descent, was first described by John Hunter,[3] who considered it to be a "fibro-muscular" cord connecting the testis to the scrotum. Its structure was elaborated in descriptions until it was said to include within it not only its own smooth muscle but also the cremaster muscle; this was believed to be inverted initially and thus able to pull the testis out of the abdomen into the scrotum. C. B. Lockwood[4] gave the foetal gubernaculum testis distal attachments or "tails," which were equated with the fibrous cords found attaching ectopic testes to their abnormal position, though he admitted that he could not find all the tails which he postulated in the foetus. Recently, however, K. M. Backhouse and H. Butler[5] showed that the gubernaculum testis is a very different structure from that described by Lockwood. They describe a structure consisting only of mesenchyme, which forms a column in the abdomen attaching the testis to the inguinal region and thence to the floor of the scrotum. The developing muscles of the abdominal wall do not encroach upon this mesenchyme, nor at a later stage of development do the fibrous tissues of the scrotal wall and abdominal fasciae. Thus this gubernacular mesenchyme is left in the inguinal canal and scrotum as a medium into which the processus vaginalis and the cremaster muscle can grow before testicular descent. When the testicle descends, the gubernacular mass expands owing to an increase of ground substance, so that it resembles Wharton's jelly, and at the same time the distal end comes to lie free in the scrotum. The scrotum and inguinal canal are dilated by this mass, and while the gubernaculum fails to grow in length relative to the surrounding tissue the testes descend. Testicular descent is, however, dependent upon a variety of changes in addition to this gubernacular swelling. It is essential for the processus vaginalis and cremaster muscle to grow down into the scrotum, and, as Backhouse[6] has shown, encroachment of fibrous tissue on the gubernacular mesenchyme can prevent this growth, thus producing anchoring bands ("tails" of Lockwood) and an ectopic testis. The vas deferens and the testicular vessels must also grow adequately in length at the correct time in order to allow the testis to descend.

The action of the steroid hormones in causing changes in the gubernaculum testis and in the associated reproductive organs is important. It is now well recognized that foetal gonads, once they have differentiated, produce their respective sex hormones under the influence of maternal gonadotrophins. The changes related to testicular descent thus appear to be controlled by maternal gonadotrophins stimulating the foetal testes to produce testosterones. In the female the gubernaculum develops as in the male until the time when the foetal ovary appears to become active, and this postulate has been given experimental support by A. Raynaud[7] working on mice and by Backhouse[8] on pouch-young opossums. These workers both showed that injections of oestrogen into the developing animal led to a cessation of gubernacular development and of growth of the associated reproductive organs.

If the testes do not descend before birth it is usual, even in normal testes, for no further descent to take place until puberty, when once again they undergo gonadotrophic stimulation, but this time from the individual's own pituitary rather than from his mother as before birth. The paper by Drs. Barbara Ward and W. M. Hunter in the *Journal* at p. 1110 this week gives further valuable statistical evidence of this phenomenon. But one important point is also evident from the figures, and that concerns the well-

[1] Moore, C. R., and Oslund, R., *Amer. J. Physiol.*, 1924, **68**, 70.
[2] MacLeod, J., and Hotchkiss, R. S., *Endocrinology*, 1941, **28**, 780.
[3] Hunter, J., in Hunter, W., *Medical Commentaries*, Part I, p. 75. London, 1762.
[4] Lockwood, C. B., *J. Anat. Physiol. (Lond.)*, 1887, **21**, 635; 1888, **22**, 38, 461, 505.
[5] Backhouse, K. M., and Butler, H., *J. Anat. (Lond.)*, 1960, **94**, 107.
[6] —— Arris and Gale Lecture, Royal College of Surgeons, 1959.
[7] Raynaud, A., *C.R. Acad. Sci. (Paris)*, 1958, **246**, 176.
[8] Backhouse, K. M., *Proc. Anat. Soc. Lond.*, February 26, 1960; *J. Anat. (Lond.)*, in press.
[9] Brunet, J., de Mowbray, R. R., and Bishop, P. M. F., *Brit. med. J.*, 1958, **1**, 1367.
[10] Linke, C. A., and Kiefer, J. H., *J. Urol.*, 1959, **82**, 347.
[11] Charny, C. W., and Wolgin, W., *Surg. Gynec. Obstet.*, 1956, **102**, 177.

known excitability of the cremaster muscle in young children. It has been said that the commonest cause of undescended testicle is the doctor with cold hands, for the contracted cremaster muscle of a child often holds the testis out of the scrotum for a long time, thus simulating cryptorchism, so that the diagnosis of undescended testicle (cryptorchid as distinct from ectopic testicle) is apt to be very difficult and time-consuming. With the onset of puberty, however, the enlarged testis can usually not pass into the inguinal canal (though it may still be pulled up into the superficial inguinal pouch), and the cremaster muscle becomes far less active; simulated cryptorchism is thus unlikely in the post-pubertal patient.

Figures of 0.41% and 0.23% given by Ward and Hunter for 14–17-year groups are high and again raise the problem of whether treatment should be left until the boy is experiencing the stresses of puberty. Recent work[9] has shown that good results can be obtained by early treatment of cases of proved cryptorchism with gonadotrophins; the accurate dosage which is now possible makes unpleasant sequelae rare. Likewise there is good evidence that early treatment may help to save some testes which might otherwise be non-functional, and the incidence of malignant change in cryptorchid testis is considerable.[10] The portents point to early treatment, and testicular biopsy[11] in doubtful cases can sometimes provide helpful information.

ROYAL COMMISSION REPORT

The Council of the B.M.A. at its meeting on March 30 decided to hold a special meeting of the Council on April 12 and a special Representative Meeting on May 19 to consider the Report of the Royal Commission on Remuneration of Doctors and Dentists in the National Health Service. As was announced in last week's *Supplement*, the Chairman of Council, Dr. S. Wand, and Mr. Holmes Sellors, Chairman of the Joint Consultants Committee, have already had a preliminary discussion with the Minister of Health.

As we pointed out in a leading article on the Royal Commission's Report,[1] the professional bodies concerned with the findings and recommendations of the Royal Commission are many and various. To co-ordinate and harmonize reactions and views of these must of necessity take some time. A precipitate decision to accept *in toto* the recommendations of the Royal Commission—even if the Government accepted them—would be little better than naive. The Council has very wisely decided to give the whole profession a full opportunity to debate the proposals of the Commission before committing the B.M.A. to a course of action which it might later come to regret. Impatience to settle the financial side of the Commission's report, without careful consideration of the future, would, the *Journal* believes, be injudicious.

It is important to separate clearly as two separate and distinct propositions what is in the Royal Commission's Report. The first are its recommendations on what doctors should be paid. The Commission recognized that it was faced with a wage claim, a recognition signalized by its suggestions for retrospective payment. Here, as our correspondence columns have shown, there are matters for elucidation and negotiation. Consultants are worried about the implications of weighting, and general practitioners about merit awards. By and large it would seem that the Commission, in its proposals, has tried to secure the spread of income recommended in the Spens Reports and a system of merit awards that will encourage the able and ambitious to take up medicine as a career.

The review mechanism proposed for the settlement of future adjustments of pay in the N.H.S. is completely separate, and should clearly be regarded as such. It is obviously illogical that consideration of this should in some way be held to be dependent upon agreement on what doctors should be paid *now* in the light of an exhaustive analysis of the changed value of money and of changes in the remuneration of other professions. That there is room for a free, perhaps prolonged, discussion on the review mechanism is shown by the fact that one member of the Commission, Professor Jewkes, dissented so far from his fellow members of the Commission that he could not agree to sign the majority report. The proposals for the review mechanism are the really significant feature of the Royal Commission's Report, because upon a satisfactory solution of the terms of reference and constitution of the Review Body will depend the future relationship between profession and Government and the evolution of the N.H.S. The review mechanism is to replace Spens. The profession must be fully satisfied that the new "charter" will provide as satisfactory a safeguard for the profession as the old one did, and at the same time preserve the freedom of the profession to take a large measure of direct responsibility for its own development. If it does not do this it will cease to be a profession and instead become a branch of the civil service. This is a grave and heavy matter, and its settlement is infinitely more important than the immediate satisfaction of financial needs. Democracy is discussion, and discussion—the Council rightly decided last week—must take place.

[1] *Brit. med. J.*, February 20, 1960, p. 556.

ANNULAR CONSTRICTIVE PERICARDITIS

Constrictive pericarditis commonly produces a generalized disorder of cardiac function, but the distribution of the constriction and fibrous thickening and the calcification of the pericardium may be irregular. Calcium may be prominent along the left border of the heart and an incomplete ring or cup of calcium in which the heart appears to be held is seen radiologically.[1]

Mounsey[2] now describes five patients in whom the main constriction was concentrated in an annular band or hoop round the pericardial sac at the level of the atrio-ventricular grooves. In four of these patients the effect was to produce generalized cardiac constriction, despite the localization of the constriction predominantly to the annulus. The fifth patient was of special interest, for signs of pulmonary, aortic, and mitral stenosis developed seven years after an operation for constrictive pericarditis. The patients were all male, their ages varying from 13 to 66 years. They showed the classical signs of cardiac constriction: raised venous pressure, with early diastolic dip, and prominent a and v (positive) and x and y (negative) waves, and an early diastolic heart sound. The electrocardiogram showed low-voltage T waves in all, atrial fibrillation in three, and right bundle branch block in one.

In two patients the degree of constriction was very severe, with very high venous pressure, considerable hepatic enlargement, and chronic pleural effusions. Fluoroscopy showed active cardiac pulsation, and in two calcification was seen in a ring around the middle of the pericardial sac.

At operation a ring of thickened pericardium was found encircling the middle of the pericardial sac, crossing the base of the heart over the conus of the right ventricle, below the pulmonary valve. This ring was calcified in two, cartilaginous in one, and fibrous in the remaining patient. The apical pericardium and that covering the body of the ventricles showed some evidence of old inflammation, but was not adherent and hardly thickened in two patients. The ventricular movement was striking, with vigorous early diastolic filling, suddenly checked by the hoop of the pericardium. When this constricting ring was cut, the ends sprang apart, especially in the patients with calcification. There was a furrow in the heart muscle beneath the band with post-stenotic dilatation distal to it. The function of the heart appeared to improve as soon as the ring was cut, and further stripping was unnecessary in two patients. The fifth patient developed signs of mitral, pulmonary, and aortic stenosis seven years after a pericardectomy for constrictive pericarditis. A second operation was performed, and a tight constricting band was found round the origin of both the aorta and pulmonary artery, with additional bands connecting it to the atrio-ventricular grooves. The aorta, pulmonary artery, atrio-ventricular grooves, and mitral area were carefully dissected free, and signs of heart failure disappeared and the cardiac murmurs became much softer. Valvular obstruction from external pressure is unusual, but both pulmonary and aortic stenosis may be simulated by tumours in the chest pressing on the great vessels. Pseudo-mitral stenosis due to pericarditis has previously been reported,[3] but pseudo-pulmonary and aortic stenosis from this cause have apparently not been described before.

The excellent results of surgery underline the need for accurate diagnosis, for without it patients with severe constrictive pericarditis are doomed. The presence of a high venous pressure with sharp negative and prominent positive waves in a patient with little cardiac pulsation, no murmurs, and an early diastolic sound should at once raise the suspicion of cardiac constriction. Pulsus paradoxus and elevation of the venous pressure on inspiration are helpful signs, and a cardiogram showing low-voltage, flat, or inverted T waves, and evidence of atrial enlargement is of additional value. The finding of pericardial calcification completes the picture. Hepatic enlargement, ascites, and oedema should be regarded as signs of heart failure secondary to constriction, and the diagnosis should always be made, and operation performed, before they develop.

In cases without calcification the diagnosis may be more difficult, for some cardiomyopathies may impair diastole owing to disease of endocardium or myocardium. In such cases the heart is often larger than in constrictive pericarditis, and an eosinophilia or other evidence of general disease may be present. Amyloid heart disease in particular may be difficult to diagnose from constrictive pericarditis without calcification. Hoarseness, dysphagia, macroglossia, and purpura may be important clues suggesting the former.[4 5] When the haemodynamic signs are unequivocally those of cardiac constriction, but a differential diagnosis cannot be made between pericardial and endomyocardial causes, then surgical exploration is warranted. Operation can cure many cases of constrictive pericarditis, for which there is no other effective treatment.

[1] Evans, W., and Jackson, F., *Brit. Heart J.*, 1952, **14**, 53.
[2] Mounsey, P., ibid., 1959, **21**, 325.
[3] Paul, O., Castleman, B., and White, P. D., *Amer. J. med. Sci.*, 1948, **216**, 361.
[4] Brigden, W., *Lancet*, 1957, **2**, 1179.
[5] —— ibid., 1957, **2**, 1243.

SELECTION AND TRAINING OF STUDENT NURSES

For a number of years now all concerned with the education and training of nurses have been pressing for the reintroduction of a minimum educational standard for students intending to become State-registered nurses. At the conference of matrons and nursing tutors held in 1958 the vote in favour of this was unanimous. The Minister of Health's agreement to the proposal announced at the end of last month will therefore be warmly welcomed. Sir John Charles, in his introduction to the Annual Report of the Ministry of Health for 1958, suggested that if more weight were given to educational attainments in the selection of candidates fewer student nurses might leave during training and the number

of those prepared to train as assistant nurses might be increased. The recently published Crowther Report also touched on this subject, remarking: "There seems little doubt . . . that the considerable amount of training that student nurses have to undertake makes it desirable that many entrants should have a full-time education until 18." The General Nursing Council has not gone so far as this, but will, after July 1, 1962, require candidates for training to have passed the General Certificate of Education in two subjects, one of which must be English (or Welsh) language: they must also provide documentary proof of the completion of a full-time education course of not less than five years and of the attainment of a satisfactory standard in five other subjects of general education. As an alternative to the formal standard laid down, there will be a special educational test devised by the General Nursing Council itself.

This proposed educational standard is indeed a minimum one, but at least it is a step in the right direction. But why have the candidates for mental and mental-deficiency nursing been left out? In view of the changes taking place both in the training of these nurses and in the care of the mentally ill, it is important that students entering these important branches of nursing should be well educated.

A nursing committee appointed by the Northern Ireland Hospitals Authority has also been considering the educational standards of girls wishing to become student nurses and the methods of selecting suitable applicants. The committee's report[1] states that it would be undesirable to reduce any further the present minimum educational standard: rather it would be better to limit the numbers coming in at this level by means of educational tests and other methods of selection, and to recruit larger numbers to the grade of assistant nurse, for which there could be a slightly lower educational requirement. The committee recommended that after 1965 all approved schools of nursing should have a standard entrance examination for candidates who had not obtained the senior or junior grammar-school certificate.

The General Nursing Council has also published the revised conditions of approval of hospitals as training-schools for nurses seeking admission to the general part of the *Register*. These will take effect from January 1, 1964. This also is a matter which has concerned the nursing profession for some time. How many nurses require the "considerable amount of training" mentioned in the Crowther Report? Those who will be capable of taking responsibility of a busy ward in a hospital, administering a hospital, training student nurses, or doing comparable work in the public-health field—all these must be well trained in all aspects of nursing. But what of those who give the day-to-day care of patients? There are many good practical nurses who can care for patients most efficiently and are happier doing so than taking responsibility for a staff or department. Such persons may well be lost to the profession with the present larger numbers of training-schools of various sizes, each trying to recruit an adequate number of trainees regardless of the suitability of the candidates. Both students and hospitals would fulfil a better function preparing for the Assistant Nurse Roll.

The General Nursing Council has proposed that a complete training-school for admission to the general part of the *Register* should have a minimum of 300 beds in one or more hospitals, and a daily average occupancy of not less than 240 beds. (At present a complete training-school is required to have a daily average occupancy of at least 100 beds.) The Central Consultants and Specialists Committee of the B.M.A., while having every sympathy with the objects of the General Nursing Council's proposals, feels that it is too drastic an increase to introduce straight away, since it is likely to remove recognition from well-established and successful training-schools and to deprive some areas of a needed training-school. It is good, therefore, to see from the circular[2] issued by the Ministry of Health that the General Nursing Council will regard the figure of 300 beds as flexible and that schools which fail by a small margin to satisfy the new requirements but which have a good record of training will not automatically lose recognition.

[1] Northern Ireland Hospitals Authority, *Report of Nursing Committee*, 1960. Belfast.
[2] Circular H.M. (60) 17

V.D. ON T.V.

Granada T.V. Network performed a public service with its factual report on venereal disease last week. The 45-minute programme, put on after 10 p.m. on March 30, was compèred—in true Gladstonian tradition—by the leader of the Liberal Party, Mr. Jo Grimond. Patients also took part. It was a successful, imaginative, and proper use of television to educate the public about a serious and growing health hazard: altogether different from some of the sensational operating-theatre scenes we have suffered from in the past. It should help to dispel the old bogy that good health education is necessarily dull.

Only two weeks earlier representatives of the Venereologists Group Committee, alive to the situation we described in these columns recently under the title "A New Epidemic of Gonorrhoea?"[3] were asking the Public Health Committee to support a public propaganda campaign "to promote the prevention and treatment of venereal disease."[4] There is still far too much ignorance on this subject, and if the mounting tide of new cases of gonorrhoea is to be reversed plain speaking is essential—particularly to the young. Here the television programme succeeded admirably. The telling comparison between the incidence of V.D. and of paralytic poliomyelitis must have jolted many people from complacency. The personal stories, recounted by the patients themselves, underlined the great importance of ignorance in the spread of these diseases: the prostitute who put too much faith in a regular "check-up," the man who said he was infected by a debutante, the homosexual who got syphilis, the boy who was infected at 15—all were examples of this. The programme was good propaganda, too, for the Special Treatment Centres. The public saw these as truly

[3] *Brit. med. J.*, 1959, 2, 685.
[4] *Supplement*, April 2, p. 185.

confidential and staffed by kind and humane people. More publicity on these lines is greatly needed.

HEALTH SERVICE ESTIMATES

Formidable as the new total cost of the Health Service is estimated to be, it is far from complete. For the estimates do not allow for whatever increases in doctors' pay are negotiated on the basis of the Royal Commission's report. After allowance has been made for the interim increases in pay, the report's recommendations, including the proposal for retrospective payments, might cost about £30m. in a full year. It is likely, therefore, that before 1960–1 is out, the gross total of the Health Service estimates for Great Britain will have passed the £800m. mark.

The estimates, however, no longer tell the whole story. From the year 1959–60 the Exchequer grants to local authorities in respect of the local health services are no longer shown in the estimates, but are wrapped up in the general grants to local authorities for all services. When the expenditure borne on the rates is included, the local health services are probably now costing at least £65m. a year.

So far as the estimates are concerned, the bill presented by them is given in the following table:

	Original Estimate 1959–60 £ Million	Final Estimate 1959–60 £ Million	Original Estimate 1960–1 £ Million
Gross total expenditure of which:	**721**	**746**	**774**
Hospital advances:			
Capital	25	24	29
Maintenance	427	443	458
General medical services	74	75	78
Pharmaceutical service	79	86	87
Dental	54	54	57
Ophthalmic	16	16	17
Less:			
Patients' payments:			
Hospitals	6	6	6
Pharmaceutical service	12	13	12
Dental	10	9	10
Ophthalmic	6	6	6
Health service contributions	112	110	111
Superannuation contributions and other receipts	38	39	45
Net cost to taxpayer	**537**	**563**	**584**

Nearly £4m. of the higher gross cost of the Service is accounted for by the supplementary employers' contribution towards the superannuation scheme. The deficit in the scheme that was reported on by the Government actuary last November is being met in part by an additional employers' contribution of 1½% of salaries for twenty years. The effect of this extra contribution extends over all the main branches of the Health Service, but it does not add to the net cost to the taxpayer because receipts from superannuation contributions show a corresponding increase.

Apart from this, the estimates show the now normal trend. Higher maintenance costs for the hospitals account for the bulk of the increase, but capital expenditure by the hospitals shows a welcome expansion. On the face of it, an estimated increase of only £1m. in the drugs bill is reassuring. But the original estimate for 1959–60 was only £79m., whereas in the event a further £7m. was found necessary. It is therefore unlikely that the new estimate will be final.

All the estimates are drawn up on the assumption that people will make no additional direct payment towards the cost of the Health Service, whether in charges to patients or in the Health Service portion of the National Insurance contribution. On Monday afternoon the Chancellor of the Exchequer announced no change in either source of revenue for the time being.

THE R.A.M.C. OF THE FUTURE

After more than twenty years conscription will soon be a thing of the past, and the Armed Forces are preparing to return to an all-regular composition. In the R.A.M.C. some changes have been made in rank structure in accord with certain of the recommendations of the Waverley Committee.[1] Promotion up to the rank of major is by length of service: promotion to lieutenant-colonel and higher ranks is by selection. The regular cadre of the future R.A.M.C. will be rather larger than it was before the second world war, and the proportion of posts in the rank of lieutenant-colonel or higher is to be almost exactly the same (42%) as it used to be. But the prospect of reaching the higher ranks is improved: the proportion of posts in the rank of colonel and above has been increased from 14% to 18%. This includes eighteen posts in the rank of brigadier, which did not exist in the old establishment. Before the war there were six posts in the rank of major-general (all non-specialist), but in certain circumstances the number could be increased by up to four supernumerary appointments for specialists. From now on the establishment of major-generals will be fixed at nine, five of whom will be non-specialists while the remainder will be the commandant of the Royal Army Medical College and three of the specialist directors at the War Office. One appointment of lieutenant-general will continue to be filled by the Director-General of Army Medical Services.

On the whole, therefore, the prospects of promotion for a doctor who decides to make the Army his career are going to be rather better than they were before the war. This is as it should be, but it is a matter for regret that four years had to elapse after the publication of the Waverley Committee's report before the future shape of the R.A.M.C. could be announced. The uncertainty about prospects in the R.A.M.C. must have hindered voluntary recruitment just at a time when it was vitally necessary to build up the regular cadre in preparation for the abolition of National Service.

The production of the index for the second volume of 1959 has been delayed. A notice will be inserted in the *Journal* as soon as the index is ready.

We record with regret the death on April 4 of Air Marshal Sir James Kilpatrick, dean of the London School of Hygiene and Tropical Medicine, and formerly Director-General of the Medical Services of the Royal Air Force.

[1] See leading article, *Brit. med. J.*, 1956, 1, 732.

Drug Treatment of Disease

THYROTOXICOSIS

BY

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The treatment of thyrotoxicosis requires both radical and palliative measures. Radical treatment aims at a partial suppression or ablation of the overactive thyroid gland. Suppression can be achieved with antithyroid drugs, and ablation either with radio-iodine or by subtotal thyroidectomy. Surgery will be mentioned only in connexion with pre-operative therapy, and to indicate where it is the treatment of choice. Some form of palliative or symptomatic treatment is usually required, at least until radical measures have taken effect. It may also be needed to control the ophthalmic, cardiac, or neurological complications of the disease.

RADICAL TREATMENT

Choice of treatment is governed by many factors. Among these are the age of the patient; the severity and duration of the disease; the size, type, and situation of the goitre; the scope and nature of any previous treatment; the kind and severity of the complications; the facilities available; and to some extent the wishes and fears of the patient after fair presentation of the various pros and cons.

ANTITHYROID DRUGS

Iodide

Until 1944 iodide was the only safe and effective therapeutic agent for blocking the release of thyroid hormone. Iodide, by ways that are still obscure, causes involution of a toxic goitre when given in relatively large amounts. Its action is rapid, increasing the storage and diminishing the release of thyroid hormone, and so lessening toxicity. Also, it facilitates the surgeon's task by reducing the vascularity and increasing the firmness of the gland. Remissions were not infrequent from its use in mild cases of diffuse toxic goitre. But in severer cases usually the effects were transient, lasting only a month or two. In toxic goitre iodide is now used only as a preparation for subtotal thyroidectomy. It is prescribed traditionally as Lugol's iodine—an aqueous solution of iodine and potassium iodide—0.3 ml. three times a day. The operation must be timed to coincide with the optimal effect of iodide on the gland, usually 14–21 days after starting treatment. Mild cases can safely be prepared for surgery with iodide alone, without risk of post-operative thyroid crisis. Severer cases should first be rendered less toxic by a 6–8-weeks course of carbimazole ("neomercazole") (see below), followed or overlapped by the standard course of Lugol's iodine.

Thiouracil and Related Compounds

Since the advent of methyl thiouracil in 1944, a number of drugs have become available for the control of thyrotoxicosis. The four compounds most widely used have been methyl thiouracil, propyl thiouracil, and more recently methimazole and carbimazole. All are reducing agents and act by interfering with the iodination of tyrosine, so interrupting the synthesis of thyroid hormone. They cause hyperplasia and increased vascularity of the gland. They are all potentially toxic.

More recently a simpler and probably much safer compound, potassium perchlorate, has been introduced for this purpose. It acts differently, by interfering with the trapping of iodide by the thyroid gland. It is now used routinely in at least one centre, and more generally as alternative treatment for those who cannot tolerate the other drugs.

Antithyroid drugs are used either in the short-term preparation of more toxic cases for surgery, or as a long-term measure. Pre-operatively, they are given for 6–8 weeks, followed or overlapped by the standard course of Lugol's iodine. Long-term treatment in adults is seldom to be recommended except in mild cases in young women without large or nodular goitres, whose disease is often transient like the emotional crisis which may precipitate it. In pregnancy it is the treatment of choice, though surgery between the third and sixth month still has its advocates. Overdosage should be avoided, for it may cause transient goitre and hypothyroidism in the baby. Thyrotoxicosis in men tends to be severe and protracted and should be tackled more radically. In children, subtotal thyroidectomy carries an increased risk of hypothyroidism later in life. For this reason treatment for at least two years with antithyroid drugs is to be recommended in the first instance, provided the goitre is not very large or does not become so during the course of therapy, in which case surgery will be required.

In general, treatment should be continued for at least 12 months. Unless there is careful selection of cases there will be a high rate of relapse on stopping the drugs, which will necessitate treatment by surgery or radio-iodine.

Carbimazole

In Great Britain carbimazole has largely replaced the thiouracil derivatives on account of its lower toxicity and a clinical impression that it causes less hyperplasia and vascularity of the gland. It is approximately 10 times as potent as methylthiouracil. The initial dose is 10–15 mg. 8-hourly, the larger dose being given only for large, nodular, or severely toxic goitres. The dose is halved after 4–6 weeks, depending on the response, and thereafter brought down at monthly intervals to the least amount which will control the disease. In mild cases this may be as little as 2.5 mg. twice a day, the more usual dose being 5 mg. twice a day, or 2.5 mg. three times a day.

Toxic reactions from carbimazole, though less frequent than from the thiouracils, are of similar nature and occur most often within 3–6 weeks of starting treatment. As with other antithyroid drugs, their incidence increases with the dose. The commonest reactions are itching, erythema, and urticaria of the skin, sometimes combined with conjunctivitis, lymphadenopathy, and fleeting joint pains simulating rheumatic fever. Though the milder reactions may be

amenable to control by antihistamines, such as promethazine (" phenergan ") 25 mg. nocte, it is nevertheless wise to switch over to potassium perchlorate for suppressing the thyrotoxicosis (see below). More dangerous toxic reactions fortunately are very rare: these include agranulocytosis, thrombocytopenic purpura, and aplastic anaemia. The drug must be withdrawn at once, and appropriate protective measures applied such as antibiotics, blood transfusion, and corticosteroids. Examination of the sternal marrow may show early regeneration before signs of this appear in the peripheral blood. The prognosis for recovery is much more favourable with agranulocytosis than the other blood dyscrasias.

Potassium Perchlorate

The therapeutic status of potassium perchlorate as an antithyroid drug is still under review. A great advantage is its low toxicity, though this increases with larger doses. Toxic symptoms consist of nausea and a maculopapular rash. Only two cases of agranulocytosis have so far been reported, but more may follow. Minor disadvantages of the drug are a tendency to cause undue vascularity of the gland, a somewhat slower action than the thiouracils, and possible interference with its action from a high intake of iodide. The recommended initial dose is 600–1,000 mg. a day in 4–5 divided doses, this being halved after 2–4 weeks.

RADIO-IODINE

Radio-iodine, first used in 1942, offers the safest treatment for thyrotoxicosis in the majority of older patients. It avoids the toxic reactions of antithyroid drugs and the disastrous surgical hazards of laryngeal palsy and hypoparathyroidism, not to mention the acute risks of laryngeal oedema and reactionary haemorrhage causing tracheal compression.

Unfortunately its use has to be restricted because of certain genetic and carcinogenetic risks, the true extent of which is not yet known. The first risk applies to pregnant women and concerns the foetus and its progeny. The second risk, to the remaining thyroid tissue, seems to be minimal, at least over an 18-year period.

Current policy in Great Britain is that therapeutic doses of radio-iodine should be given only exceptionally to patients under 45 years of age whose mean life expectancy would exceed 20 years. In those over 45 it is the treatment of choice for: (1) diffuse toxic goitre; (2) toxicity recurring after previous subtotal thyroidectomy; (3) very nervous patients who fear surgery; (4) patients with severe thyrotoxic heart disease or other debilitating conditions, after adequate preparation with antithyroid drugs.

With toxic nodular goitres the rate of recurrence after radio-iodine is higher than with diffuse toxic goitres, and several courses of treatment may be required. For this reason, and because malignancy cannot always be excluded in these patients, there is still a case in older patients for subtotal thyroidectomy by a surgeon experienced in this operation, especially if the goitre is large or unsightly. Solitary toxic nodules and toxic intrathoracic or sublingual goitres are best treated surgically; the last two lesions may swell during exposure to radio-iodine.

There are several relatively minor disadvantages of treatment with radio-iodine. First, the patient must be admitted to a radiotherapeutic unit for about one week. Secondly, it is hard to estimate the dose precisely. This is attempted by formulae based on (*a*) the amount of a preliminary tracer dose of radio-iodine taken up by the gland, and (*b*) the weight of the gland, which cannot be determined with any accuracy. The ideal dose should result in neither myxoedema nor recurrence of thyrotoxicosis; yet in practice the incidence of these sequelae is quite high.

The outcome depends partly on how evenly the dose is taken up by the gland, for areas of thyroid tissue which are inactive at the time of treatment may later hypertrophy and cause toxicity. This is especially so with toxic nodular goitres, and these may need repeated treatments with radio-iodine. Thirdly, radio-iodine corrects toxicity more slowly than thyroidectomy or antithyroid drugs: at least three months must elapse before the patient becomes euthyroid. Severely toxic patients, and those with advanced thyrocardiac disease, cannot safely wait that long and will need preliminary treatment with antithyroid drugs.

Treatment with radio-iodine is justified only exceptionally in patients under 45, the main indications being recurrence of thyrotoxicosis after subtotal thyroidectomy, and severe cardiac or other associated diseases.

PALLIATIVE AND SYMPTOMATIC TREATMENT

Sedation

Until thyrotoxicosis has been corrected, most patients will benefit from sedation and a hypnotic at night. In doubtful or borderline cases it is wise to defer definitive treatment until the outcome is clearer; little is to be lost from a period of observation and sedation with amylobarbitone mg. 15, two to three times a day, combined with a sympathetic and reassuring psychological approach.

Malignant Exophthalmos

Several hormones or their synthetic analogues have been used in attempts to suppress the pituitary, the *vis a tergo* believed to be responsible for this dreaded complication. Whether the pituitary factor is overproduction of thyrotrophic hormone, or, as seems more likely, of an associated exophthalmic substance (E.P.S.), is not yet clear. The unpredictable natural history of the complication makes the task of therapeutic assessment very difficult. Testosterone and oestrogens have been abandoned, and thyroxine in large doses now has few advocates, in the treatment of the condition. It is, however, generally agreed that, when severe exophthalmos threatens, any sudden reduction or overcorrection of thyrotoxicosis is dangerous, presumably because it stimulates further secretion of thyrotrophic hormone or E.P.S. The patient needs repeated reassurance and should be kept at a mildly hyperthyroid level by careful undertreatment with antithyroid drugs for at least six months, or until the outcome is clearer. Some consider the addition to the regimen of laevo-thyroxine 0.4 mg. a day to be a prudent safeguard against the risk of therapeutic hypothyroidism. If the patient has in fact been allowed to become hypothyroid, then the rapidly acting thyroid hormone, tri-iodothyronine, should be prescribed in doses of 0.04 mg. twice a day for two to three weeks until laevothyroxine has had time to take effect.

If exophthalmos rapidly worsens, despite careful management, there should be no delay in applying such measures as lateral tarsorrhaphy, radiotherapy to the orbits or pituitary gland, and, as a desperate sight-saving measure, orbital decompression (Naffziger's operation). Corticosteroids equivalent to a daily dose of 100 mg. cortisone may assist in reducing the orbital oedema. The eyes should be protected with oily drops and shielded by dark glasses.

Cardiac Complications

The most common cardiac complications of hyperthyroidism are auricular fibrillation or flutter and congestive failure; these are the reactions of an ageing heart to the long-sustained demands of increased cardiac output. Other lesions of the heart may be present coincidentally. Thyrotoxic heart disease steadily increases in incidence from middle age onwards. Recognition of it is a signal for early treatment, for its reversibility depends to some extent on the duration of symptoms.

Until their thyrotoxicosis has been corrected, patients in congestive heart failure should be treated by bed rest and the appropriate cardiac therapy, depending on the severity of the condition. Those with uncomplicated auricular fibrillation will require digitalization only if the heart rate is rapid. If the cardiac rhythm does not revert to normal very shortly after hyperthyroidism has been corrected, the use of quinidine should be considered. Severely toxic patients may respond poorly to digitalization, but overdosage must be avoided.

Muscle Wasting

In the older age-group thyrotoxicosis occasionally presents with severe wasting of muscles, simulating myopathy or myositis. In this event, one of the new anabolic steroids, such as "durabolin" (19-nortestosterone phenyl propionate), 25 mg. once a week by intramuscular injection, may assist return of strength, alongside radical treatment.

Glycosuria

Transient glycosuria is not uncommon in thyrotoxic patients. It may be due to a lag in storage of glucose consequent on rapid absorption from the gut, or to unmasking of a mild latent diabetes by increased metabolism. The condition usually responds to treatment of the underlying disease. If diabetes is severe, or persists after treatment of the thyrotoxicosis, it should be controlled by the usual measures.

Thyroid Crisis

This dreaded and often fatal complication is rarely seen these days. It erupts when the circulating thyroid hormone reaches a critically high level in patients already exhausted from their disease. Most often it is precipitated by surgical manipulation of a toxic goitre inadequately prepared for operation. There is no way, unfortunately, of neutralizing thyroid hormone once it has escaped into the blood-stream, and its degradation is very slow. All that can be done is to prevent further release of the hormone by promptly giving iodide in large doses, and protecting against its effects by digitalization, sedation, and corticosteroid therapy; for there is some evidence that adrenocortical exhaustion may be an important factor in these cases.

ASSESSMENT OF APPLICATIONS FOR REHOUSING ON MEDICAL GROUNDS

BY

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The housing problem in certain areas is still a long way from solution. It has considerable public-health implications, and it places heavy responsibilities on the medical officer of health, who must assess the degree of priority to be awarded to applicants furnishing medical certificates in support of their rehousing claims. The number of these certificates has increased steadily in the London area since the war. Many patients believed that the greater the number of certificates the more priority was obtained and the quicker the rehousing. Though this was not so, it was difficult to explain the real situation to them. The variety of certificates submitted was considerable and their value and accuracy were sometimes obviously doubtful. It was clearly necessary for some regulation to be introduced to produce conformity and a substantial measure of fairness in allocating priority, and also to allow the family doctor a chance to give his objective recommendation confidentially. Argles (1950) drew attention to the increase in the number of rehousing applications; he showed that, whereas in 1938 the number received by the L.C.C. was 1,000, by 1949 (first nine months) it had risen to nearly 23,000. He observed that some applicants used every means in their power to secure accommodation and that the medical certificate was the most favoured method of gaining some preference.

Between 1955 and 1958 the Borough of Camberwell received 3,235 applications for rehousing; during the same period 1,623 housing applicants claimed medical priority. The applications were accompanied by certificates from the family doctor and to a lesser extent from hospital doctors and almoners.

In a review of 1,028 applications for rehousing, supported by medical certificates, submitted to Hampstead Metropolitan Borough, Warren (1954) found that 25% related to respiratory infections, 15% to rheumatic disorders, and 14% to psychological disorders. He stressed the need of the medical officer of health, in awarding "medical points," to have detailed information about the housing and medical conditions before he can allocate points.

After consultations with general practitioners and hospital staffs it was decided to introduce in Camberwell a new system that should prove more equitable. It was agreed that the form of medical certificate for housing should be the same for all cases and that only one certificate should be submitted for each patient unless the medical condition changed.

The Certificate

In 1955 the accompanying housing form was devised and brought into use.

BOROUGH OF CAMBERWELL

CONFIDENTIAL No.....

APPLICATION FOR PRIORITY REHOUSING ON MEDICAL GROUNDS

For Official use only	
Recomm.	Date

PART I

Name of applicant.....

Address .....

PART II To be completed by MEDICAL PRACTITIONER

Name of patient..... Age.....

This patient suffers from.....

As a result of your visits, what housing features do you consider adversely affect this condition?

.....

.....

.....

Bearing in mind your knowledge and experience of other cases requiring rehousing, into which of the following categories of medical priority should this patient's name be placed

1. Most urgent.....
2. Urgent .....
3. Soon .....
4. No priority .....

Date..... Signed.....
Medical Practitioner

It is regretted that no fee can be paid for this certificate

PLEASE RETURN FORM IN THE ENCLOSED STAMPED ADDRESSED ENVELOPE

PART III To be completed by PUBLIC HEALTH INSPECTOR

(a) Family for whom accommodation is required:

.....adults

..... male children aged.....

.....female children aged.....

(b) Present accommodation:

Room	Living-room	Bedroom	Scullery	W.C.
Number				
Floor				
Whether shared				

Total persons..... Equivalent number.....

Total number of rooms..... Permitted number.....

Statutory overcrowding?.....

(c) Standard of present accommodation:

1. Is separate sleeping room available for patient(s)? .....
2. Is there serious dampness? .....
3. Is water supply readily accessible? .....
4. Any other serious defects? .....
5. CAN POINTS BE AWARDED FOR BAD CONDITIONS? .....

(d) REMARKS: .....

Date..... Signed.....
Public Health Inspector

RECOMMENDATION BY MEDICAL OFFICER OF HEALTH

I recommend that this application should be placed in the following category of medical priority:

1. IMMEDIATE .....
2. URGENT .....
3. LESS URGENT .....
4. NO RECOMMENDATION.....

Date..... Signed.....
MEDICAL OFFICER OF HEALTH

Part I shows that a responsible person makes the application. Part II is the information given by the family doctor, and the answers show without doubt or possibility of confusion from what the patient is suffering and how this condition was affected by his or her present dwelling. It was expected that the practitioner signing the certificate would have visited and seen these conditions. The practitioner is then invited to assess in which of four grades the amount of priority the patient and the condition warrant, bearing in mind his knowledge of other cases and applications. It was fully realized that most practitioners were not always aware of statutory or accepted standards. Part III is usually completed by the public-health inspector before the certificate reaches the doctor, who is therefore in the happy position of knowing whether there is any statutory overcrowding or structural defect recognized by the borough, and he does not have to rely on the patient's own statements.

Assessment of Certificates

It was felt that a panel should be set up to review the certificates and decide the assessment of priority in one of the four categories. The panel consisted of the medical officer of health, a medical consultant, and a general practitioner. The Table opposite gives an analysis of the results of the 1,623 assessments made.

Discussion

The system described has proved to have many advantages. The special form which gives general practitioners accurate information on overcrowding and sanitary circumstances was appreciated by them: its introduction was followed by a marked reduction in the number of "medical" applications; indeed, in a number of cases the form was returned with the recommendation "no priority." This was hardly possible previously when the doctor handed his certificate to the patient.

Many "medical reasons" given by patients themselves are groundless. However, we found a fair measure of agreement between the assessment of the family doctor and that of the panel, using this method of arbitration. There was also some progressive diminution in the number of applications in which the panel gave a lower recommendation than the general practitioner.

In addition to the personal medical category, the description of the environmental conditions found by the public-health inspector (see Form, Part III) was of great benefit in arriving at the final priority.

Many remediable housing defects were discovered *pari passu* and appropriate action taken.

Dampness was cited in support of some 159 cases (10%). After public-health inspectors' visits, confirmation was obtained in 137 of these.

Overcrowding.—The family doctor gave evidence of this in 305 cases. Confirmation by public-health inspectors was made in 280 of these and notification of statutory overcrowding was then sent to the housing authorities concerned. However, the limits of statutory overcrowding are by no means liberal and many borderline cases are seriously affected. It is natural that

HOUSING APPLICATIONS FOR MEDICAL PRIORITY JULY, 1955, TO DECEMBER, 1958

Classification by Types of Disease, and Priority Given by Applicant's Own Doctor and by the Panel

Disease	General Practitioner				Panel				Total	% of Total
	1	2	3	4	1	2	3	4		
Tuberculosis	31	49	88	65	35	47	83	68	233	14·4
Functional nervous disorders	54	123	128	18	21	71	118	113	323	19·9
Bronchitis (excluding tuberculosis)	43	104	94	25	16	79	88	83	266	16·4
Cardiovascular	20	52	28	3	13	49	22	19	103	6·3
Diseases of bones and joints	15	35	42	8	6	39	38	17	100	6·2
Organic diseases of the nervous system	16	20	13	—	10	18	14	7	49	3·0
Pregnancy	5	14	6	3	2	14	5	7	28	1·7
Diseases of the digestive system	1	11	11	3	—	10	7	9	26	1·6
Other*	13	44	30	11	7	30	33	28	98	6·0
Unclassified diseases	2	39	44	36	2	34	48	37	121	7·5
Died, gone away, forms not returned; rehoused; no residential qualifications	—	—	—	—	—	—	—	—	276	17·0
Totals	200	491	484	172	112	391	456	388	1,623	100·0
% of total	12·3	30·3	29·8	10·6	6·9	24·0	28·1	24·0		

* Defective sight, blood dyscrasias, senility, neoplasms, skin conditions, poliomyelitis paralyses.

family doctors should believe overcrowding to exist even though by reason of the age of the children the legal limits are not exceeded.

Disabilities

Tuberculosis.—A special points system for tuberculous applicants was devised in 1953, and this, with some modification, has proved successful and has been continued (Chalke, 1953). By this method of assessment, families at the greatest risk by reason of the age and sex of the members, and adverse living conditions, were given the highest priorities. The outmoded and often only criterion of "positive sputum with no separate bedroom" has thus been considerably modified. The special forms were completed at the chest clinic and the number of points calculated at the same time. This simplified the work of the panel, and no instance occurred in which the recommended and the final assessment of priority differed. Fourteen per cent. of all recommendations were in respect of tuberculous disease.

Nervous Disorders.—In 20% of the applications the disability was given as mental illness—chiefly nervous debility or anxiety neurosis. These cases presented the biggest assessment problem, for, while in a number of instances the effects of malhousing were very real, in others there were no grounds for believing that this was so, or indeed that the diagnosis could be accepted as anything but an attempt (for which we had much sympathy) to accelerate rehousing. In these cases the opinion of consultant psychiatrists was invaluable, though unfortunately rehousing could not be assured in all the deserving cases.

Bronchitis.—Bronchitic patients formed the second largest number (16.4%) of applicants. Dampness (though its presence was not always confirmed) was often alleged to be a causative or aggravating factor.

Accidents.—In a previous study (Chalke and Watton, 1959) the value of public-health inspectors' visits in remedying defects was shown. In addition to their routine and statutory visits, these specific housing inspections in respect of medical priorities gave the inspectors opportunities for giving householders much advice.

Friction.—This was an aggravating factor in 75 applications. The problem of young couples sharing houses and flats with "in-laws" or of two women being forced to use a common kitchen occurred frequently.

It became obvious that the "colour bar" problem was increasing in south-east London. Examples quoted included coloured and white tenants in adjacent rooms having to share W.C. accommodation. The purchase of a house by a coloured person caused resentment amongst the white tenants, many of whom had lived there for a number of years; it was often alleged that there was victimization in order to evict them in favour of coloured tenants, the latter often being willing to pay higher rents.

Exchange of Accommodation

Even when no overriding medical factor could give a priority, in 74 cases (5%) simple exchange was recommended. Usually the need is for ground-floor accommodation—for example, old people or persons with locomotor difficulties. In many instances the provision of such exchange would release additional housing units. This aspect of rehousing, though it is administratively complex, merits more attention; its wider application would be advantageous.

Summary

Details are given of 1,623 applications for rehousing priority on medical grounds in a London borough.

A form used for assisting the general practitioner in making a recommendation is described. It is shown that the difficult task of awarding priorities at a time when applications are numerous and available houses limited is best undertaken by a panel, on which the medical officer of health has the assistance of a consultant and a general practitioner.

Doctors are, however, becoming increasingly aware of the difficult housing situation, and of the necessity for taking it into account when giving a medical priority. When they appreciate this to the full, a final assessment by an independent medical panel will cease to be required.

Our thanks are due to Dr. J. M. K. Marsh, consultant in chest medicine, Camberwell Hospitals Group, for his assessment of the tuberculous applicants and for his invaluable help as a member of the panel.

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MENTAL HOSPITALS OF THE FUTURE

NATIONAL ASSOCIATION FOR MENTAL HEALTH

The National Association for Mental Health held its annual conference on March 24 and 25 at Church House, Westminster. The theme for this year—World Mental Health Year—was "Mental Health at Home and Abroad." The conference was opened by the Minister of Health, Mr. DEREK WALKER-SMITH, and the Home Secretary, Mr. R. A. BUTLER, took the chair at the morning session on the second day, when "The Future Role of the Hospital" was discussed. This session is reported below. Other sessions were on "The Importance of British Experience in the World Mental Health Scene" (chairman: Sir AUBREY LEWIS), "The Medico-social Problem of the Psychopath" (chairman: Lord COHEN OF BIRKENHEAD), and "Lessons of the Community Care Services" (chairman: Dr. J. A. SCOTT).

Mostly Dismal Buildings

Mr. BUTLER opened the session on the future role of hospitals by paying tribute to those who voluntarily carried out mental-health work. There was little doubt, he said, that in this age everyone tended to depend too much upon the State agency and upon huge institutions. Without the voluntary work in the mental-health field progress would be impossible, and a great debt was owed to those who engaged in it.

Dr. H. F. OSMOND (physician superintendent, the Saskatchewan Hospital, Canada) said that the majority of mentally ill people in most parts of the world were cared for dismally, and at least one reason for that dismal care was the wretched buildings in which they were housed. He gave examples of three psychiatric hospitals built between 1860 and 1960—one a well-known British hospital, another his own hospital in Saskatchewan, and the third an American mental hospital—all of which, he said, clearly had in common a disregard of human beings and human values. The urge to impress and show off had blotted out any other thought. They were three vignettes, variations in the horrible, from brass and lino to stainless steel and vinyl, in terms of pseudo-Gothic, bogus Georgian, and stereotyped functional, with hardly a single original idea between them. Those hospitals developed their bizarrities not through any lack of psychiatric or architectural knowledge, but from something much more deplorable—a failure to heed what was perfectly well known.

A properly run mental hospital could not have for its goal anything less than the best hospitals had a century or more ago—that is, to return as many people as possible to their homes and to independent life outside the hospital. What was needed was a building in tune with the goals of a particular hospital and the function it served. Dealing with one mental illness—schizophrenia—and its relationship to mental-hospital design, Dr. Osmond expressed the view that schizophrenics needed hospitals specially designed to allow them to learn how to cope with outside society. Evidence strongly suggested that, once they could deal with a very small group of people, they were quite well enough to be placed outside the hospital, and that should be done without delay. Hospital buildings could play their full part only if the needs of patients were diligently studied, he concluded, and very close collaboration between the architect, psychologist, psychiatrist, and the other people concerned was necessary.

Architect and Medical Superintendent

Dr. E. S. STERN (medical superintendent, Central Hospital, near Warwick) said it was evident that more money would be spent on mental hospitals, and it was to be hoped that they would receive the adequate and serious attention of boards and committees. Any scheme of building would fail unless there was full consultation between the architect on the one hand and the medical superintendent and his staff on the other *before* any plan was put on paper and at every stage until the completion and handing over of the building.

Dr. Stern expressed some doubt whether there would be a large permanent increase in the number of mental beds in general hospitals, although there was a case for facilities in general hospitals so that when a patient developed mental symptoms he could still be retained. Mental beds in a general hospital were bound to be comparatively few, and that gave rise to a sense of hurry in treatment so that the bed could be cleared for the next occupant, which was bound to encourage—sometimes prematurely—drastic methods in the hope of a quick result, when the patient's principal requirement might be for prolonged rest and persistent psychological help.

The need for special hospitals for disturbed adolescents was becoming more widely acknowledged, continued Dr. Stern, and doubtless accommodation for them would become general. To some extent there was already such accommodation in schools for difficult children, including Approved Schools, but the latter by their very nature were a little rigid, and it was a pity that they were tied to the legal system and juvenile courts. "We must realize that the mental-deficiency hospital is becoming increasingly a place of education and treatment, and less one of incarceration," concluded Dr. Stern. "Hence, greater use will be made of admission for short periods of intensive training, especially in the low-grade patients who are maintained at home."

Proper Use of Space

Mr. R. LLEWELYN DAVIES (director, Division for Architectural Studies, Nuffield Foundation), speaking from the point of view of the architect, said it was necessary to get architects to the point where they really understood what went on in mental hospitals and what the patients needed. One of the requirements which were conspicuously missing from the older type of mental hospital was variety in the use of space. There should be freedom to use different kinds of spatial circumstances suitable to the particular care being applied. Another requirement was that the layout should be comprehensible, to get over the difficulty which patients experienced in understanding and relating space. The older type of hospital was particularly incomprehensible, for it consisted of a repetition of identical spaces.

Mr. Llewelyn Davies emphasized that the type of mental-hospital building which was wanted would not come about unless those who commissioned and instructed the architects knew a certain amount about architecture and unless a number of architects knew a good deal about the work of mental-health hospitals. Architecture needed the opportunities for postgraduate research and training which most other professions had developed. An architect could hardly be expected to tackle successfully the design of mental hospitals from a background unconnected with work in the mental-health field. In the future there must be joint research projects in which the architect worked with the users of the buildings.

During 1959 a series of articles by Dr. CICELY SAUNDERS on "Care of the Dying" was published in the *Nursing Times* and reprints have now been issued by Macmillan's (price 2s.). The articles are written with a strong sense of the dignity of human nature and provide a compassionate and objective account of the help that can be given to alleviate the physical and spiritual discomforts of a patient at the end of his life. Dr. Saunders trained as a nurse at St. Thomas's Hospital during the war, took a degree in politics, philosophy, and economics at Oxford, and became an assistant almoner at St. Thomas's in 1947. Her interest in the problems of terminal illness led her to read medicine, and she qualified in 1957. She was awarded a three-year fellowship in the department of pharmacology, St. Mary's Hospital Medical School, for research in analgesics and in the treatment of patients who are dying.

Nova et Vetera

HISTORY OF THE R.C.S.

This official history of the Royal College of Surgeons* begins with the separation from the Barber-Surgeons Company, which, through the influence of Thomas Vicary, had been established by Act of Parliament in 1540. Another Act of Parliament dissolved from June, 1745, the old union and established a new corporation: "the master, governors and commonalty of the art and science of Surgeons in London." John Ranby and William Cheselden were active in effecting this change. In 1751 Surgeons' Hall in the Old Bailey was built. John Hunter's name through his work and the Hunterian Museum is imperishably associated with the College, but he was too busy with his scientific researches and "earning that damned guinea," to take an active part in its administration, though he was a member of the Court of Assistants. In 1796 the Company of Surgeons dissolved because a master was elected without a proper quorum. In 1800 the surgeons' difficulties were solved by an appeal to the Crown, and the Royal College of Surgeons in London was established by Charter of King George III. In 1822 a supplementary Charter replaced the Master and Governors by a Council with a President and Vice-presidents. The new College had been built in Lincoln's Inn Fields. The history of the library and museum are well described in two special chapters, the library by Mr. W. R. LeFanu, the librarian, and "John Hunter's Museum'" by Miss Jessie Dobson, the anatomy curator.

Sir Zachary records the progress of the College from strength to strength: the founding in 1843 of the Fellowship which has come to be regarded as the highest of surgical distinctions; the new Charter this advance necessitated, the title being changed to the Royal College of Surgeons of England; the bearings of the Medical Act of 1858; the birth of the dental profession; the fight for the admission of women; the Conjoint Examination; the discussions with London University; the effects of the first world war. He notes how Lord Moynihan encouraged the revival of research, aided by bequests and gifts such as those of Sir G. Buckston Browne. The College has also been fortunate in having had such eminent comparative anatomists as Sir Richard Owen, Sir Arthur Keith, and Professor Wood-Jones in its service.

In the latter part of the book the history is told of the bombing of the College in the second world war, and how, under the able Presidency of Lord Webb-Johnson, success was reborn out of disaster, with the help of munificent bequests, including those of Lord Nuffield, its honorary Fellow and gold medallist. The College has, in fact, become a University of Surgery with its own faculties and professors. Its postgraduate teaching and research activities attract increasing numbers of students, many from the British Commonwealth and from other countries overseas.

This is a great book which reflects equal credit on the College and on its distinguished historian. It is well produced and copiously illustrated. The dust cover has a reproduction in colour of the coat-of-arms of the College and a portrait of the author.

ARTHUR S. MACNALTY.

GIAMBATTISTA DELLA PORTA AND THE SEGRETI

When 25-year-old Giambattista della Porta formed an "academy" at Naples in 1560 he was but doing no more than what hundreds of his countrymen had done, and were to do, throughout the century. Like them, he gave it a strange name: the Accademia del Segreti, or Academy of Secrets. Even stranger and more fantastic names had been chosen by other academy founders: the Lunatici (also of Naples), the Extravaganti, the Fulmiales, and of the Chaff (della Crusca). Nor was it the first academy to turn its attention to science, for an academy had been instituted seventy-five years earlier at Milan to nourish arts and sciences. Indeed, the total number of Italian academies during the century runs well into three figures. Why were the Segreti so different? The answer is that each member was obliged to have made a significant discovery in physical science. This reflected della Porta's own interests, manifested in a book he had published two years before the society was formed: *Magiae naturalis, sive de miraculis rerum naturalium libri iiii.* This manifesto, translated into French, Italian, and German, evoked in Italy the charge of witchcraft. Though he cleared himself of the charge before the Inquisition, this charge was repeated some years later. This, coupled with the names and the activities of the Segreti, evoked hostility and they were suppressed.

But della Porta was not to be discouraged. Under the patronage of Cardinal Luigi d'Este he travelled around the Italian peninsula. In 1580 he manufactured at Venice a parabolic mirror. He undertook chemical and biological research. Amongst his numerous subsequent works was *De humana physiognomia* (1586), a strange and exciting book. It shows the analogies of humans to animals. Some of its plates are curious anticipations of Lavater and Sheldon. Meanwhile his *Magiae naturalis* was brought up to date with a confutation of witches, a treatise on magnetism, and an account of the camera obscura. He disputed with Campanella, the noted Jesuit utopist; wrote a rural encyclopaedia; and in 1593 explored the application of mathematical techniques to biological phenomena.

Such imaginative "experimentation," given wide currency by his ready pen, won him disciples. A Frenchman, N. C. F. de Peiresc, came to visit him, and returned to France to found a similar group. In Porta's own home town of Naples his work was intermittently revived, by Stigiola, who worked on refraction, and by physicians like Tomaseo Cornelio and Lionardi di Capoa, who used to meet in the house of Marco Aurelio Severino (1580–1656), a skilful surgeon and anatomist. Severino's skill found ample scope in 1610 in the diphtheria epidemics of Naples, when he practised tracheotomy. Severino's use of refrigerants to dull pain won acceptance, whilst his use of comparative anatomy in *Zootomia Democritae* (1645) was characteristically in the tradition of the Segreti.

Inspired by della Porta's *Magiae naturalis*, Prince Federigo Cesi of Rome established in 1603 the Accademia del Lincei. This took (from the *Magiae naturalis*) as its emblem the sharp-eyed lynx. Indicating its filiation, Cesi came down to Naples to establish a branch organization, of which della Porta became president. The Lincei planned to operate with botanic gardens and laboratories, and to publish their proceedings. They published two of Galileo's early books. The members—numbering 32—carried on experiments on their own account. The Academy of the Lynx lived up to its name, for the first systematic observations with the microscope are generally held to be those of one of the original four members, Francisco Stelutti on honeybees in 1625.

By 1609 the Lincei had a German group, a Roman group, and a Florentine group. The German group included G. Schreck, G. Faber, M. Welser, and T. Muller; the Roman group included C. Muti and V. Cesarini; and the Florentine group included F. Salviati, Galileo's disciple, who appears as a character in Galileo's *Dialogue concerning Two Chief World Systems* (1632) and the *Discourses on Two Sciences* (1638). Galileo had joined the Lincei in 1611 and was probably encouraged by them to publish *Letters on the Solar Spots* (1613). Galileo was first warned by the Catholic Church in 1615, the year of della Porta's death.

Della Porta's devotion, though primarily to physics, spread over many fields. He wrote on the force of steam (a pioneer work), on fortifications, on distillation, and on

(*Continued at foot of next page*)

**The Royal College of Surgeons of England. A History.* By Zachary Cope, Kt., F.R.C.S. (Pp. 360+xii; illustrated. 63s.) London: Anthony Blond. 1959.

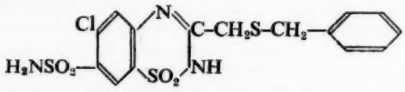
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Benzthiazide

"Fovane" (Harvey Pharmaceuticals).

Chemistry.—Benzthiazide is 3-benzylthiomethyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide. It is a derivative of chlorothiazide and has the following structural formula:



Pharmacology.—Benzthiazide by its action on the renal tubules has a diuretic action leading to increased excretion of sodium, chloride, and water. It also increases potassium excretion; and the electrolyte pattern of the urine with respect to sodium, chloride, and potassium shows no consistent difference from that after administration of chlorothiazide, hydrochlorothiazide, or hydroflumethiazide. It resembles hydrochlorothiazide and hydroflumethiazide in having little effect on bicarbonate excretion.

Therapy.—Benzthiazide is supplied as 50-mg. scored tablets, and can be given for the relief of oedema in cardiac failure, hepatic cirrhosis, renal disease, premenstrual tension, toxaemia of pregnancy, and when water retention occurs as a consequence of steroid therapy.

The dosage range for initial treatment is 50–200 mg., depending on the degree of oedema, and for maintenance therapy 25–50 mg. The drug should be given as a single dose in the morning, and to minimize loss of potassium intermittent treatment on alternate days or twice weekly is advisable. Benzthiazide may also be used to potentiate the hypotensive effect of reserpine and ganglionic-blocking agents.

The drug appears to have an action similar to, if not identical with, that of other benzthiadiazines, and cannot, therefore, be considered a therapeutic advance.

Contraindications and Toxicity.—Experience with this diuretic is still limited, but toxic effects have not so far been reported. Benzthiazide does, however, increase the excretion of potassium, and may therefore be expected to induce coma in patients with ascites due to severe cirrhosis of the liver. It will also increase the liability to digitalis intoxication in cardiac failure.

N.H.S. Basic Price.—100 50-mg. tabs. for 58s.

(Continued from preceding page)

telescopes. As if this were not enough, he wrote three tragedies (only one of which survives), 29 comedies (of which 14 survive), and one tragi-comedy. He was the Italian Francis Bacon; a trumpeter calling others to combat.

The Segreti and the Lincei were prototypes for later groups, like the German Academia Naturae Curiosorum (in 1652) and the Florentine Accademia del Cimento (in 1657). Their persistent quest for knowledge of the physical world, married to the anatomical investigations of Padua, did much to hasten the evolution of physiology. For when the famous medical school at Padua utilized the techniques of Segreti and Lincei they were able to explain the mechanical functions and apparatus of the body. Symbolizing this fruitful marriage, Santorio, born in the year after the Segreti was formed, published his famous *De Medicina Statica* in 1614, the year before della Porta died.

W. H. G. ARMYTAGE.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Conservative Treatment of Ulcerative Colitis

SIR,—The fears expressed by Dr. R. W. Cockshut (March 5, p. 731) concerning the development of carcinoma in ulcerative colitis are well founded. We have recently published our conclusions following an extensive study based on an analysis of 304 cases of cancer developing in patients with ulcerative colitis.[1] Of these patients 72% have already died, and only 4.2% of the remainder have so far survived to five years following surgery. In 112 patients sufficient detail was available to permit statistical analysis; the calculated expected survival rate of every case followed to five years was 18.6%. Of the 304 patients who developed cancer 34 did so in retained colon following previous ileostomy or caecostomy: in two cases cancer arose in the remaining bowel after previous segmental resection: in 11 patients a growth developed in the remaining rectal stump after previous ileostomy and colectomy, and three further cases developed cancer in the remaining rectum after ileoproctostomy. Latterly two further instances presented of carcinoma developing in a rectal stump after ileoproctostomy. Thus of 306 cases with cancer 52 underwent a previous surgical procedure for ulcerative colitis with incomplete eradication of diseased bowel.

We note that Mr. Stanley Aylett accepts (March 19, p. 876) the risk of the development of neoplasia and agrees on its lethal characteristics; nevertheless he feels that retention of the rectum is permissible, since "total colectomy and ileorectal anastomosis will effect a cure, the disease in the remaining rectum resolving once the whole of the ulcerated colon has been excised." This is not invariable, however, as was shown by a case Mr. Aylett reported in a review of 120 cases treated by ileoproctostomy.[2] "One patient has developed cancer of the rectum. He was aged 19 at the time of operation and had had colitis since the age of 2. The rectal inflammation *failed to resolve* after total colectomy and ileorectal anastomosis." The rectum is diseased in not less than 95% of cases; we believe that it should therefore be removed in the treatment of ulcerative colitis.—We are, etc.,

GEOFFREY SLANEY.
BRYAN N. BROOKE.

Department of Surgery,
Queen Elizabeth Hospital,
Birmingham.

REFERENCES

[1] Slaney, G., and Brooke, B. N., *Lancet*, 1959, **2**, 694.
[2] Aylett, S., *Proc. roy. Soc. Med.*, 1959, **52**, Suppl. p. 24.

Dumping Syndrome

SIR,—With reference to the recent article by Mr. M. Hobsley and Mr. L. P. Le Quesne on the effect of insulin in the dumping syndrome (January 16, p. 147), we have used tolbutamide on a 62-year-old male patient who has had typical dumping syndrome since a subtotal gastrectomy in January, 1957.

The patient presented with drowsiness, a sensation of epigastric distension, borborygmi, and nausea after meals. These symptoms were so incapacitating that he found it difficult to continue with his work and had lost much weight.

We found that 10 units of soluble insulin 15 minutes before lunch prevented these symptoms following that meal, but that they occurred after the evening meal. With a view to more consistent effect at least inconvenience to the patient, tolbutamide was tried. With 1 g. of tolbutamide at 6.30 a.m. he was completely free of drowsiness or borborygmi throughout the day, while his abdominal discomfort was diminished. The blood-sugar values were also less variable.

Blood-sugar Estimations Following Similar Meals at 12 Noon and 3 p.m.

Time	10 Units Soluble Insulin at 11.45 a.m. (mg./100 ml.)	1 g. Tolbutamide at 6.30 a.m. (mg./100 ml.)
11.30 a.m.	71	73
Noon	61	68
12.30 p.m.	110	101
1.00 ,,	191	157
2.00 ,,	97	101
3.00 ,,	81	79
4.00 ,,	280	171

After two months of continued therapy, appetite was improved and he had gained 7 lb. (3.2 kg.) in weight. He is still free of his more distressing symptoms.

It would be of more interest to assess this treatment with further patients. Pre-operative investigations of candidates for partial gastrectomy might demonstrate some existing tendency to lag storage, comparable with the small proportion of patients who subsequently develop the dumping syndrome.—We are, etc.,

M. R. CAPON.
A. R. TAPPIN.

King Edward Memorial Hospital,
London, W.13.

Psychogenic Disorders in Children

SIR,—I fail to understand the reason for the controversy emanating from the excellent paper by Dr. John Apley and his co-workers (January 16, p. 191). May I ask the evidence for the statement in the letter by Drs. Edith M. Booth and Dermod MacCarthy (March 26, p. 968) that "almost every paediatrician would agree that to *treat* psychological illness is definitely beyond his scope"? How many paediatricians were asked for their opinion before this conclusion was reached? Surely every paediatrician should treat all those behaviour problems which he is competent to treat—competent because he is interested in them, has extensive experience of them, has read widely about them, and knows by following up all children treated by him that his treatment is successful. No one would suggest that the paediatrician should refer every child with a cardiac murmur to the cardiologist, every child with a joint symptom to an arthrologist, or every child with a neurological abnormality to the neurologist. Why should he refer every child with psychological problems to the psychiatrist? The paediatrician has to be a general physician, and treat the whole child.

As in all branches of medicine, it is essential to know when one does not know—when to ask for expert advice. In the same way with psychological problems, the paediatrician must know when a particular problem is beyond his scope. If the paediatrician passes all behaviour problems on to psychiatrists, the latter will inevitably be so cluttered up with trivial disorders that they have no time to treat really important problems which they alone are competent to treat, and cases in which treatment is urgent (such as acute school phobia with absenteeism). All children have behaviour problems, some more than others, and it seems to me obvious that a paediatrician must be able to treat them. Dr. Apley and his colleagues are to be congratulated on the work which they are doing.—I am, etc.,

R. S. ILLINGWORTH.

Department of Child Health,
University of Sheffield.

Boys on Probation

SIR,—I read with interest your annotation (*Journal*, March 5, p. 715) concerning D. H. Stott's work in Glasgow on boys on probation.

But it seems academic at the present time to try to pick out the delinquency-prone boys when we have inadequate facilities for dealing with those already known. This point is surely underlined by the findings of the Durand inquiry into the recent disturbances at the Carlton Approved School.[1] This showed that a significant number of boys needed psychiatric attention, and it would also appear that staff members would have found discussion of difficult problems with a psychiatrist useful. Even those approved schools which have a visiting psychiatrist often have so little of his time that the service can only be described as a skeleton one.

And when we come to deal with the more highly disturbed adolescents there is difficulty in finding suitable in-patient facilities for them when these are needed. They are not always suitable for the ordinary mental hospital regime, and their behaviour may make them unwelcome in such a setting. So before we try to find more patients we should, perhaps, give some thought to the problem of who is going to treat them, and how are the special units which are necessary to be provided. —I am, etc.,

W. H. ALLCHIN.

London, S.W.5

REFERENCE

[1] Disturbances at the Carlton Approved School on August 29 and 30, 1959. Report of Inquiry by Mr. Victor Durand, Q.C., December 31, 1959. Cmnd. 937. London, H.M.S.O. 1960.

Paediatric Prescribing

SIR,—As an orthopaedic surgeon responsible for the treatment of patients of all ages with acute osteomyelitis, I feel I must disagree with Professor Wilfrid Gaisford. In "Paediatric Prescribing" (March 12, p. 794) he advises the use of penicillin, 1–2 million units twice daily, in the treatment of this disease.

In our review[1] of 206 cases of acute osteomyelitis from the Booth Hall Children's Hospital in 1955 we found 12% of infections were insensitive to penicillin. We also pointed out at that time that "effective therapy offers its best protection if commenced within twenty-four hours." Delay in effective treatment results in a rapid rise in bone abscess, sequestration, and all the troublesome or even disastrous sequelae of the disease. In reviewing 46 patients admitted between January, 1958, and August, 1959, organisms were recovered in 27. Fourteen of these proved to be staphylococci insensitive to penicillin.

It is clear from these figures that about half the patients will not benefit from penicillin therapy. To use this agent is to delay effective treatment for a large number of patients in the vital first forty-eight hours. All proved or suspect cases of acute osteomyelitis should be treated by a wider-spectrum antibiotic at the earliest possible moment, and it is then justifiable to change to penicillin if a sensitive organism is recovered later.—I am, etc.,

C. H. CULLEN.

Booth Hall Hospital,
Manchester, 9.

REFERENCE

[1] Cullen, C. H., and Glass, A., *J. Bone Jt Surg.*, 1955, 37B, 722.

SIR,—I was interested to read Professor Wilfrid Gaisford's comments on treating the allergic child with antihistamines (March 12, p. 794). I presume that under this heading the main conditions he would include would be eczema, asthma, hay-fever, and urticaria. It would seem generally accepted that this series of drugs can reduce the degree of hay-fever and urticaria, but the action on asthma and eczema is debated. One of the difficulties in assessing the effect has been that the mild sedative side-actions of the drugs may be beneficial in the type of child commonly treated.

In deciding whether antihistamines will have a specific action on one of the disorders it is often advisable to use, as a control, small doses of sedatives rather than inert preparations. I reported a series of cases[1] which were compared in this way and drew the conclusion that antihistamines had no specific action in eczema, with the exception of a group of uncommon cases in which the reaction appeared to be a mixture of eczema and urticaria. Since then further experience has supported this report. If, therefore, we use the drugs in treating eczema we are largely using them as sedatives and we should use those antihistamines which have a more pronounced and regular sedative side-effect, such as diphenhydramine hydrochloride (" benadryl ") and promethazine hydrochloride (" phenergan "). If, on the other hand, we wish to treat hay-fever or urticaria and the side-effects of the drugs are undesirable, we should use an antihistamine with the greatest specific effect and the least side-actions, such as chlorcyclizine hydrochloride (" histantin ") and chlorpheniramine maleate (" piriton ").

In recent years it seems to have become the custom to recommend trying one antihistamine and, if it is not effective, switching to another, suggesting that different antihistamines are likely to affect the disorder in different ways and that such therapy is a " hit-and-miss " venture. This has arisen in part from comparing the drugs not given in equi-effective doses, which in continued therapy are roughly diphenhydramine hydrochloride 300 mg., promethazine hydrochloride 50 mg., mepyramine maleate (histantin) 600 mg., chlorcyclizine hydrochloride 150 mg., and chlorpheniramine maleate 12 mg. Also the disorders treated are likely to fluctuate in severity and therefore be affected to a greater or lesser extent by the same dose of the drug; a change to another drug may coincide with such a fluctuation and thus an erroneous impression of its action is gained. Apart from confusing the physician's assessment, a change in the type of antihistamine, associated with spontaneous improvement in the disorder, makes the patient believe that particular drug is better and from then on the effect of the drug is potentiated by " suggestion."

The specific action of antihistamines, in at any rate urticaria, appears to be the same with all the range of drugs, and it is only the incidence and type of side-effects which will vary from patient to patient. In practical therapy, if the response to average doses of one of the more powerful antihistamines is not enough, it would seem better to increase the dose rather than switch in a haphazard way to another antihistamine.—I am, etc.,

Bristol. ROBERT P. WARIN.

REFERENCE

[1] Warin, R. P., *Brit. J. Derm.*, 1950, **62**, 159.

Congenital Dislocation of the Hip

SIR,—In support of the plea for early diagnosis of congenital dislocation of the hip, it might be of interest to report the results of an early diagnosis campaign carried out in the East Fife area of Scotland. The number of cases discussed is small, but in view of the geographical situation and administrative arrangements in this particular area the statistical findings are reasonably accurate.

During the 18 months' period prior to an early diagnosis campaign, 10 cases of complete dislocation of the hip were discovered. The diagnosis was established by arthrogram examination and the patients were treated by frame reduction in hospital followed by operation. The importance of early diagnosis was stressed in talks given to nursing and medical personnel dealing with the post-natal period in that area. During the next three years only one dislocation occurred, but 25 infants were diagnosed in the predislocation and early subluxation stages. These 25 infants were all treated successfully by conservative methods as out-patients.

East Fife Area

	1954 (1½ Years)	1956 (3 Years)
Dislocation	10	1
Subluxation	0	10
Predislocation	0	15
	10	26

The campaign for early diagnosis was based on the detection of abnormal thigh and buttock skin-creases or limitation of hip abduction. All children with a family history of congenital dislocation of the hip were also referred for *x*-ray examination during the first few months of life. The diagnosis was established by *x*-ray examination as judged by the acetabular angle and the alignment of the upper femur in relation to the socket. Approximately 50% of the infants referred for *x*-ray examination were not considered to have any definite hip pathology.

Space does not permit discussion of other interesting relevant factors, but the results would suggest that early diagnosis in the predislocation and subluxation stages is possible with the co-operation of those supervising the post-natal period.—I am, etc.,

G. P. MITCHELL.

Princess Margaret Rose Orthopaedic Hospital, Edinburgh, 10.

Thyroiditis

SIR,—Dr. Deborah Doniach, Mr. R. Vaughan Hudson, and Dr. I. M. Roitt refer to the mumps-virus induced-thyroiditis in their excellent paper in the *Journal* of February 6 (p. 365). May I add my twofold experience of thyroiditis complicating infectious mononucleosis? Two brothers-in-law, one of them a physician, had the same course of this actually rather frequent infection: both presented a subacute type of thyroiditis. Though the sensitiveness of the gland disappeared but slowly and the general malaise of the patients lasted four to five weeks, the objective signs of transient hypothyroidism subsided and no damage whatever in the thyroid function remained.—I am, etc.,

Hospital Bajcsy-Zsilinszky, Budapest, Hungary. L. MOSONYI.

Auto-immunity

SIR,—Your lucid leading article on thyroid disease (February 6, p. 407) boldly employs the term " auto-immune " and suggests a sinister role for antibodies in yet other diseases. The phrase " auto-immune " is inaccurate and inelegant, yet it has become fashionable and even respectable.[1] This is not surprising, since the concept is as alluring as that of focal sepsis and perhaps we have slipped the leash of logic and yielded to the magic of a name.

While most prefer to believe that thyroid antibodies are concerned with gland destruction one cannot be completely sure that they are not otherwise employed in the physiological function of phagocytosis of extravasated colloid. The evidence for cytotoxicity rests, firstly,[2] on those now classical experiments which produced glandular lesions in animals injected with thyroid extract, and, secondly,[3] on the recent fascinating demonstration of the effects of "Hashimoto" serum on thyroid cells in culture. Although this evidence is formidable it is not altogether immune to gentle criticism.

Firstly, one cannot be sure just how closely the experimental thyroid lesion resembles Hashimoto's disease (as described by Dr. Hashimoto), because this comparison has so far escaped searching pathological inquiry. The experimental lesion is not easy to produce and should be distinguished from the non-specific, round-cell infiltration to which the thyroid and possibly the adrenals are susceptible following the application of diverse stimuli. The refreshing discovery of cytotoxicity in tissue culture is rendered perplexing by the demonstration[4] elsewhere of the ability of thyroid cells to flourish in certain concentrations of stored serum rich in thyroid antibodies. These observations are not necessarily contradictory but rather emphasize the importance of the cytotoxic substance, which may possess a much wider significance than is generally realized.

The frequency of liver pathology[5] in Hashimoto's disease is difficult to assess, but in seven necropsy cases I have found no hepatic lesions whatsoever. The finding of complement-fixing "antibodies" when organ extracts other than thyroid are used does not clarify the situation. The auto-immune complement-fixation test yields quite high titres in the serum of some patients with Hashimoto's disease when human liver is used as antigen. Since this test also gives positive reactions in entirely different conditions—e.g., biliary cirrhosis—one wonders if it does in fact measure an antigen-antibody reaction. The mixing in test-tubes of complex tissue extracts such as adrenal with the serum of the sick is a popular pastime, but the finding of agglutination, haemolysis, or precipitation does not necessarily permit us to deduce that the reaction has an immunological basis even though it is demonstrated by a serological method. Does the fixation of complement by the Wassermann reaction imply that the acquisition of syphilis is a manifestation of hypersensitivity? As Professor E. Kabat[6] once pointed out, if the spirochaete of syphilis had not been discovered, then to-day many would regard the disease as an example of auto-immunity.

The concept of auto-immunity is by no means new, and nearly all ailments of mankind, even old age, have at some time been ascribed to auto-antibodies. It seems certain that the future will see an avalanche of antibodies descend upon us, and in particular antibodies directed against body constituents—e.g., certain mucins with which the cells of the reticulo-endothelial system are "unfamiliar." Clearly it is now time to consider the criteria by which we should decide whether these modified globulins are constructive or destructive. Whilst it goes without saying that all are indebted to the workers in this field, we should perhaps adopt a more cautious attitude to "auto-immune disease" and follow the example of Mr. Spectator, who, when asked if he believed in ghosts, replied that "he preferred to suspend his belief."—I am, etc.,

Paris. A. E. STUART.

REFERENCES

[1] Burnet, M., *Brit. med. J.*, 1959, **2**, 645, 720.
[2] Witebsky, E., and Rose, N. R., *J. Immunol.*, 1956, **76**, 408.
[3] Pulvertaft, R. J. V., Doniach, D., Roitt, I. M., and Hudson, R. V., *Lancet*, 1959, **2**, 214.
[4] Irvine, W. J., "An Investigation of the Pathogenesis of Hashimoto's Disease by Tissue Culture Methods," Prize Essay, Univ. of Edin. Library.
[5] Luxton, R. W., and Cooke, R. T., *Lancet*, 1956, **2**, 105.
[6] Personal communication.

Asepsis on T.V.

SIR,—I feel that Professor T. Anderson's letter (March 19, p. 882) cannot be allowed to pass without comment. In the Royal Navy I immunized thousands of individuals, using a 20-ml. syringe and changing the needle. I have never read of, or can imagine, any way that this could be dangerous. To use the word malpractice, without substantiating it, is, I feel, to quote, "reprehensible."—I am, etc.,

Longtown. G. M. INGALL.

Fatal Diphtheria after Immunization

SIR,—We read with interest Dr. Guy Bousfield's letter (*Journal*, February 13, p. 498), and noted his valuable criticisms on our article entitled "Fatal Diphtheria in the Fully Immunized Child" (*Journal*, January 23, p. 251). We thoroughly agree that it was a mistake to have given antidiphtheritic serum without first having taken blood for antitoxin estimation, but, in extenuation, we would like to point out that the history, as originally presented to us, described the child as never having been immunized. It was only subsequently, on going carefully into the records, that we discovered that the child had, in fact, been immunized as described in our article.

There was no record that a successful result had been confirmed either by a Schick test or by blood antitoxin titration, which raises the important question: would it not be advisable to Schick-test all children who have received the standard diphtheria inoculations to ensure that they really are immune?

With regard to Dr. Bousfield's third paragraph, we agree that pneumonia may well have taken precedence over toxic myocarditis in causing the child's death, although where two grave factors are operating it is never easy to say which takes priority in determining the fatal outcome. Certainly we would not have expected pneumonia by itself to have caused death, and the rapid circulatory collapse towards the end suggested that myocardial involvement was a prime factor. In the light of Dr. Bousfield's objection to the title of our article, we are rather puzzled that he mentions in his last paragraph that he had seen a similar case in a *fully immunized child* (our italics). Could it be that he intended "A Child who had Received Immunizing Injections"?—We are, etc.,

W. N. DUNNET.
E. M. SCHALLIBAUM.
T. G. SCOTT.

Royal Free Hospital, London.

Alopecia, Urticaria, and Stress

SIR,—It is difficult to know what one should make of Dr. Margaret Reinhold's paper (March 19, p. 846) on the relation of stress to alopecia areata and chronic urticaria. Indeed, had the author made more use of her material it would be possible to assess her findings more satisfactorily. In view of her comment that the selection of patients depended on the views of the dermatologist referring the patient, it would have been helpful to know what proportion of the total attendance of these two dermatoses was in fact seen by the psychiatrist. If they were selected because of the presence of obvious psychiatric symptoms, it can come as no surprise that these were present in 100% of cases

submitted to a full psychiatric examination. But what about the patients who were not referred?

Dr. Reinhold breaks down her patients into six groups depending on the emotional circumstances at the time of onset of the dermatosis. It is permissible to wonder about the criteria for assessing whether a "stress" is major or minor. From the examples given it is difficult to decide. Case 2 is placed in the category of "long history of stress and minor crisis." But is the loss of a wife by desertion followed by "an appalling row" with the patient's brother to be regarded as a *minor* crisis? Case 3 is placed in the "long history of stress without obvious crisis" group. The patient's alopecia developed after the desertion of his alcoholic wife, and a relapse occurred when the patient was, to use the author's words, in a state of "extreme unhappiness and frustration at work." Case 6 is placed in the group of psychological disturbance but no stress. This man's hair fell out after being told after some months of training as a teacher that he was temperamentally unsuited for teaching and should look for another job: no stress?

In the urticaria group we are told that *major* crises do not appear to be precipitating factors. A patient is then described who developed urticaria when she realized that her much-loved, only daughter had a sarcoma from which she would die. I can see no reason to class such a tragic discovery as a minor crisis.

On the subject of treatment Dr. Reinhold is somewhat non-committal. As she says that she wanted to study the effects of *adequate* psychotherapy, one hoped for some assessment of this difficult problem. Instead, we are told that no conclusion can be drawn, as the spontaneous recovery rate of these two dermatoses makes it impossible to assess the result accurately. The six failures were all cases of alopecia totalis, a condition notoriously resistant to treatment. Had we been given data of the duration and extent of the alopecia in all cases it might have been possible to derive some knowledge of the usefulness of psychotherapy. A case of some years' standing, resistant to accepted modes of treatment, who grew a satisfactory head of hair after a few months of psychiatric treatment would be acclaimed by some as a triumph for psychiatry. Unfortunately Dr. Reinhold is silent on this very pertinent information.

The author is less than just to Macalpine's careful study of alopecia[1] when she implies that the psychogenic theory of this disease was rejected because of lack of response to psychotherapy. Certainly this point was discussed, but Macalpine bases her thesis for the rejection of the psychosomatic concept largely on the histories of her patients. No formal or frequent relationship between emotional disturbance and onset of alopecia was noted in her patients, who sometimes developed it without preceding mental shock, who had mental shocks without developing alopecia, and where previous attacks of alopecia temporally related to mental shock did not recur when equally severe mental trauma was experienced.

Dr. Reinhold concludes by saying that in certain cases stress plays a part in the causation of alopecia areata and chronic urticaria: but in which cases? Goodness knows, it is difficult at any time to be absolutely certain about the relationship of an emotional event to the progress of a psychosomatic illness, but in skin cases it should be possible to plot the relapses or remissions against the psychiatric state of the patient with some degree of accuracy. In some of Dr. Reinhold's cases such associations were observed and it would have been useful to have greater details about these patients.

The absence of control studies makes the author's conclusion even more tentative. Had her cases been a random sample, and had they been compared with a similar sample of other skin cases, the incidence of psychiatric symptoms in each group could have been compared and more definite conclusions reached. In the absence of such studies I feel that the case for psychogenic aetiology of alopecia areata is unproved. Chronic urticaria is a different matter, as already there exists a fair agreement that emotional factors are important. One wishes that Dr. Reinhold had told us more about her cases where psychiatric causality appeared fairly certain.—I am, etc.,

Newcastle upon Tyne, 4. F. A. WHITLOCK.

REFERENCE

[1] Macalpine, I., *Brit. J. Derm.*, 1958, **70**, 117.

Spiritual Healing in Hospitals

SIR,—I share the surprise of your correspondents from Deva Hospital (March 26, p. 962) that "spiritual healers" are to be allowed to roam the wards of our hospitals. The terms of their code of conduct certainly do not inspire confidence. I am relieved, however, to read that if they consider a joint should not be immobilized they are advised "not to tell the patient about it."

May we soon expect to see a flood of lay hypnotists, Christian Science practitioners, or naturopaths all likewise invading the wards? However sympathetic their attitude, and however careful they are to touch the patients "outside the blankets," they might cause a good deal of confusion to the patients and disruption of hospital routine.—I am, etc.,

London, E.2. D. E. PEAKE.

SIR,—The admission of spiritualist healers to State hospitals must alarm those who stand for rationality in dealing with rational man. There cannot, however, be any doubt but that spiritualism offers to satisfy an intuitive desire in mankind for a healing which is not confined to atomistic materialism.

There is a rational spiritual healing proclaimed by the trinitarian Christian Church, of which the rationality is expressed scientifically by Max Planck and Einstein in *unified field theory*, psychologically by Carl Jung, and philosophically by Plotinus and Schweitzer. Only last year Arthur Koestler published his book *The Sleepwalkers*, in which he charged academic science with remaining bound by Newtonian atomism when the door to field theory had been open for 50 years. In this theory the materialization of the ultimate particle of matter is the product of intelligent will—hence Max Planck speaks of a mentoid atom and Raynor Johnson (a physicist and principal of a university college) speaks of a psychoid electron.

I write to suggest that it is only because academic medicine has refused to admit, and because institutional religion has refused to operate, a spiritual healing which is God-given and rational, that the barriers are now forced by a misguided public opinion, and by an irrational technique. It is not too late for Christians within the Health Service to demonstrate by their actions that only the rational is good, and that, if man is body, soul, and spirit, he needs healing of all his three parts. Since we already believe in specialization, let us be consistent and call in the Church both "to proclaim the Coming of the Kingdom and to heal the Sick" in partnership with doctors who also are agents of His reconciliation.—I am, etc.,

London, W.14. GRIFFITH EVANS,
Consulting Surgeon to the Presbyterian Healing Ministry in Wales.

SIR,—Few of our colleagues will disagree with the letter on Spiritual Healing (March 26, p. 962) and signed by members of the medical staff of the Deva Hospital, Chester. On first thoughts it seems that the medical men on the various management committees of our hospitals have let us down and been stampeded by the lay members. But on second thoughts there seems no need to panic. These spiritual healers are not coming into our hospitals to displace us, nor are they coming in to interfere with either the medical or the surgical procedures. They are merely sick-visitors coming in at the request of the patient to pray for healing power to be given. Rather than discourage these few people we should welcome them provided their credentials are vouched for by some responsible body. Healing is not an exclusive right of our profession. We should always be ready to examine other means of healing that may be complementary to our methods.

This gift of spiritual healing is not new. It goes back to earliest times. It was practised by the ancient priests and medicine men, and long before the Christian era there were established all over Greece healing sanctuaries built in honour of the legendary god Aesculapius who healed the sick, blind, and the suffering and brought the dead back to life. The pages of history abound with stories of remarkable cures by certain individuals, who were sometimes learned Church dignitaries and sometimes unlearned lay persons. This healing power was practised by the followers of Jesus, Buddha, and Mohammed with equal success.

In opening our hospitals to spiritual healers to come in at the specific request of our patients, we have an opportunity of finding out whether such patients are restored to health and strength quicker and more permanently than other patients who are not being helped by spiritual healing.—I am, etc.,

Bearsden, Glasgow. JOHN WINNING.

SIR,—In your issue of March 26 (p. 962) a letter is published from nine doctors from Deva Hospital, Chester, deploring the fact that 117 hospital authorities have given permission for accredited members of the National Federation of Spiritual Healers to attend patients in hospitals when requested to do so, subject to medical assent. The number of hospital authorities who have now given this permission is 235—there have only been 29 definite refusals throughout the United Kingdom.

The objection of the signatories to this letter is that we " have little or no real understanding of the medical ethics involved or indeed of the fact that the practice of medicine rests on a scientific basis." They admit that we are anxious to avoid arousing criticism from the medical profession, as indeed we are, and we have taken precautions to avoid offending medical ethics. We recognize that medical treatments rest upon scientific bases, and hope that doctors will appreciate that spiritual healing treatments conform to spirit science—which needs to be co-operative with physical science.

It is not my purpose to justify in this communication the claims of spiritual healing, but I refer to the conclusions in the B.M.A.'s report on *Divine Healing and Co-operation Between Doctors and the Clergy*[1] and *The Church's Ministry of Healing*[2] that through spiritual healing " recoveries take place that cannot be explained by medical science."

It cannot be denied that through spiritual healing recoveries take place, sometimes contrary to medical expectation, and our only purpose is to enable the sick to be helped in this way so that they may receive advantage from both forms of treatment. Spiritual healing and medical practice, while differing fundamentally, are complementary to each other, and it is difficult to understand why any doctor should wish to deny to a patient the aid we can give.

The signatories urge their fellow members to seriously consider " whether or not they can enter into any kind of professional association " with spiritual healers. I do not think we are seeking " professional association " ; all we are asking is for doctors to allow our co-operation in a purposeful way for those who are sick. This would not interfere in any manner with medical practice —possibly it may do much to help it.

I am correct in stating that the policy of the British Medical Association is to co-operate with spiritual healing (see the reports I have mentioned) ; and surely allowing our accredited members to attend the sick is putting the policy into practice.—I am, etc.,

HARRY EDWARDS,
President,
National Federation of Spiritual Healers.

REFERENCES

[1] *Divine Healing and Co-operation Between Doctors and Clergy*, 1956. British Medical Association, London.
[2] *The Church's Ministry of Health*, 1958. Church Information Board, London.

New Drugs for Depression

SIR,—Dr. Douglas Goldman (March 12, p. 805) appears not to have read our letter (January 16, p. 200) very carefully. We stated specifically that our Case 1 received *unmodified* E.C.T. There is, therefore, no possibility that this collapse was attributable to suxamethonium. We are, of course, familiar with adverse reactions to suxamethonium ; these are of two types—immediate cardiac collapse, fortunately rare, and delayed respiratory embarrassment, which is relatively common. The collapse noted in our two cases did not resemble either of these pictures, but consisted of delayed cardiac and respiratory collapse. In our experience, cardiac involvement only occurs in delayed respiratory embarrassment due to suxamethonium, if adequate oxygenation is not maintained. We therefore do not accept Dr. Goldman's suggestion that the reaction in our Case 2 was due to the suxamethonium.

We are not convinced that the intravenous administration of atropine has all the advantages claimed, and find it possible by careful timing to avoid serious errors in the atropine-treatment interval. However, even if we accept Dr. Edwin McH. N. Dunlop's statement (February 27, p. 647) that our technique is faulty and old-fashioned, it is a remarkable coincidence that collapse after treatment should have been a very rare complication of our E.C.T. before we started using phenelzine. The dose of phenelzine given in our Case 1 was 15 mg. three times daily. This is certainly not an overdose. The makers' original recommendations suggested a dosage of 75 mg. daily, whilst work quoted by them contains references to doses of up to 90 mg. daily. On this basis, our dose of 135 mg. daily in our Case 2 was not three times the recommended dose as suggested by Drs. Dunlop and Goldman, but less than twice. However, King[1] used a standard dose of 50 mg. three times daily in his series.

If Dr. Goldman thinks it is hardly relevant to attribute the respiratory embarrassment to phenelzine

when the drug had been discontinued six days previously, we suggest that our alleged overdose is no more relevant. It is our belief that when new drugs are being tried under hospital conditions where a close watch can be kept for toxic effects, it is fully justifiable to exceed the recommended dosage. If the dose of chlorpromazine originally recommended had been strictly adhered to, many schizophrenics who have been able to return to their homes would still be in hospital.—We are, etc.,

F. A. BLEADEN.
G. CZEKANSKA.

Bracebridge Heath Hospital,
Lincoln.

REFERENCE

[1] King, P. D., *Amer. J. Psychiat.*, 1959, **116**, 64.

Mothers' Preference in Confinement

SIR,—Presumably we are interested to know the preferences of women with respect to home and hospital confinements in order that we may have guidance in our efforts to provide the best service compatible with both medical requirements and the mothers' wishes.

The strongest arguments for hospital confinement are often medical ones, but these are rarely appreciated by the mothers (and often not by doctors where a question of relative risks only is involved). They are most strongly influenced by "atmosphere," separation from family, etc., and it is not surprising that many find the hospital atmosphere and separation from a young family unbearable. Maternity hospitals are too often not the havens of rest and peace we would like them to be, but surely rather than accept this as an argument for more home confinements we should direct some thought and effort to improving the hospital atmosphere. Is it really necessary that mothers should be awakened at five, that they should be awakened by others in labour, and that they should rarely see their babies, to mention only a few faults in too many hospitals? If the short stay in hospital advocated by some becomes general, separation from family would be a less weighty argument for home confinements.

Recording mothers' preferences in one area is not going to be really helpful elsewhere unless it can be assumed that the hospital atmosphere is the most congenial possible and that the domestic nursing services, etc., are the best that can be provided. At present neither can be assumed with confidence.—I am, etc.,

J. H. E. BAINES.

Weeping Cross,
Staffs.

SIR,—We should like to make a few observations on Sir Dugald Baird's letter (February 27, p. 642). He suggests that the Ilford and Blackpool surveys, though superficially fair and reasonable, are by no means representative. So far as we were concerned in Blackpool our survey was directed entirely to those mothers who had had an opportunity of experiencing confinement in hospital and at home. It was considered that their opinions were more likely to be valid than primiparous women who had had no opportunity of forming an opinion of the place of confinement. We do not dispute the fact that the majority of births occur in hospital, but it is important to differentiate between an opinion expressed by a mother and what is expedient in the mother's interest regarding place of confinement.

Dealing with the comment on the third commonest response in the Ilford survey, which was the second commonest in Blackpool—i.e., "individual attention at home"—he states that good medical and nursing care, whether at home or in hospital, recognizes the importance of the individual. This may be true in most hospitals, but certainly not all. In discussing the problem of questioning, we tried to avoid the pitfall of direct interrogation and asked every mother to complete the form herself in her own time. The latest results in our survey follow very closely those we reported in your correspondence columns on January 30 (p. 349).—We are, etc.,

D. W. WAUCHOB.
D. P. W. ROBERTS.

Municipal Health Centre,
Blackpool.

Pathology for the G.P.

SIR,—Dr. S. L. Henderson Smith says (*Brit. med. J.*, March 5, p. 725) that he is unable to get post-mortem examinations performed on patients under his care dying at home. He may be interested to know that I perform regular examinations for general practitioners on cases of especial interest both here and at Sevenoaks. The management committee has agreed to cover the cost of transporting the body from home, making private arrangements with a local undertaker and accommodating it at the hospital mortuary. No other charge is involved. We consider this to be a reasonable part of a comprehensive hospital pathology service for general practitioners.—I am, etc.,

KEITH J. RANDALL.

Department of Pathology,
Orpington Hospital,
Kent.

Hypnotic Suggestion in Domiciliary Midwifery

SIR,—Serious workers in the field of hypnosis and obstetrics will read, largely with regret, the correspondence that has so far taken place on the subject. I am engaged on a research project to evaluate its place in domiciliary midwifery. Having used hypnosis for several years, I am aware of its pitfalls and limitations as well as its undoubted usefulness in correctly chosen cases.

It may be said that there are roughly five categories of patients: (1) Those who are unhypnotizable. (2) Those who do not want to be hypnotized. (3) Those who achieve light or medium trance and, unfortunately, have little proved benefit in labour though they may achieve benefit during pregnancy. (4) Those who achieve some relief in labour. (5) Those who have a pain-free labour. The statistics for each group are not yet available for domiciliary midwifery, but it seems probable that the first three groups constitute the large majority of patients on any doctor's list.

Hypnosis in the past (as indeed relaxation) has been bedevilled by extravagant claims which have not stood up to the test of scientific proof, and it would be a pity if we allowed our natural enthusiasm for a useful procedure to make us put forward claims that, as yet, are unsubstantiated and, in the light of present evidence, may well be untrue. The main points made by Dr. A. Fry in his letter (February 20, p. 569) have not, to my knowledge, been scientifically proved unless there are some unpublished statistics to which he has access. To take the point, for example, that mothers who have gone through a delivery under hypnosis "gain permanently in self-confidence": this may well be true, but is it true? How is self-confidence measured? Is it not true that most mothers, after a successful labour, "gain(s) permanently in self-confidence"? Hence, presumably, his

controls gain in self-confidence less than his successfully hypnotized subjects. The same point could be made of blood loss and obstetric shock.

Again Dr. R. A. B. Rorie (February 20, p. 569) states that hypnosis is the "only safe anaesthetic." There is, I believe, a lot of truth in this. But the patient who is tremendously keen to use hypnosis and, when attempting this in labour, finds that it is of little or no benefit, may go through an emotional crisis which needs very careful handling—especially if extravagant claims have been made to her in advance. She may not only lose confidence in her doctor but also, and much worse, in herself.

It is with these questions in mind that present research is being conducted. It is hoped to be able to tell a pregnant woman early in her pregnancy whether or not hypnosis can be effectively used in her case, and also to try to increase the number of patients (in my experience a minority) who can get a substantial benefit from hypnosis during labour. It is therefore important that those who have been working in this field for some years should beware of making extravagant claims which can only discourage other doctors when they discover that they cannot successfully hypnotize the majority of their patients so that they have a pain-free labour.

Surely co-operation between midwife, general-practitioner obstetrician, and consultant must be achieved, but not, as Dr. J. W. F. Lumsden (January 30, p. 350) would suggest, by hypnosis alone. Such co-operation is necessary whether hypnosis is used or not, though hypnosis in suitable cases can be a useful joint field of work. However, we are a long way from abandoning anaesthetic machines or drugs or both—or hypnosis for that matter—they all have a part to play in successful labour, a part that needs constant evaluation and revaluation in the light of current experience and statistics.—I am, etc.,

St. Paul's Cray, Orpington. P. A. L. CHAPPLE.

Spontaneous Deep Hypnosis

SIR,—An increasing number of doctors are using hypnosis, either as an aid to psychotherapy or more superficially in obstetrics, dermatology, dentistry, etc. Few dangers exist, and most books stress the apparent innocuousness of the method. Recently a phenomenon occurred in one of our patients which might give beginners a certain amount of difficulty.

A woman aged 36 had been treated eight years previously by extensive psychotherapy and drug abreaction, for insomnia of seven years' duration. Abreaction revealed to her that she had been raped at the age of 21, but she could not tell the psychiatrist this, and broke off treatment with him. She was then treated by a medical hypnotist, whom she told of the episode, which, incidentally, had been doubly traumatic as it had culminated in an attack of venereal disease.

Following this revelation she was apparently cured and remained well for four years. At this time her husband committed suicide, following which she relapsed into insomnia. She now saw one of us, and further questioning in the waking state revealed that she had an affair with a married man following the death of her husband. This appeared to be the precipitating factor for the relapse, allied with the previous sexual trauma. She was easily hypnotized to a medium state and told these facts. Hypnosis was then terminated, and she opened her eyes and smiled. The hypnotherapist turned his back to open the curtains in his room, turned round again, and approached her. She immediately and spontaneously went back into obvious somnambulism and refused to come out of the state. Explanation that she wished to remain in hypnosis for fear of returning fully to reality, together with reassurance that reality would now be more acceptable and that she would be able to sleep, coupled with firm instructions to open her eyes on counting down from "five" to "one" resulted in her waking. She seemed dazed, and waited 20 minutes before being allowed to go home.

This case would appear to be unique, for there has been no previous description of a person being hypnotized, the state being terminated, and then there occurring a spontaneous return to a deeper level of hypnosis.

Space will not allow us to discuss the possible psychodynamics involved, but it is as well to remember that spontaneous hypnosis at the deep level, although rare, is a phenomenon that must be expected in every hypnotherapist's life. Analysis of the reason for not wanting to give up the state must be undertaken immediately, otherwise the patient should be left to "sleep it off," which is tedious and difficult in practice. The danger of using hypnosis by unqualified persons for purposes of helping people to pass driving tests, examinations, etc., is therefore obvious, and the Hypnotism Act of 1952 fails in this respect. The banning of stage hypnotists has not prevented the subjection of individuals to equal hazards at the clinical level, and this aspect must be seriously considered, by the proper authority, in the very near future.—We are, etc.,

GORDON AMBROSE.
GEORGE NEWBOLD.

London, W.1.

More Dysentery

SIR,—At a time when the incidence of bacillary dysentery, already high, is increasing in many parts of the country, including London, your well-considered leading article (April 2, p. 1034) is appropriate and most helpful. It contains two observations, however, which appear to require some comment.

You draw attention, very rightly, to the need for special precautions at schools and other centres of infection; and you go on to say that it *may* be necessary to organize supervision of hand-washing routine. Since washing of the hands is *the* basic principle in the prevention of excremental diseases, such supervision would seem to be obligatory. You remark, also, that it *may* be helpful to substitute paper towels for roller towels as a temporary measure. Surely, Sir, the use of the old-fashioned roller towel should not be countenanced anywhere, at any time—certainly not in a school or institution in which cases of bacillary dysentery are occurring. The roller towel of this type is as much a relic of the unhygienic past as the open drain and shallow well.—I am, etc.,

London, S.E.5. H. D. CHALKE.

Eaton Agent

SIR,—The recent paper on infection with Eaton's primary atypical pneumonia (P.A.P.) agent by Dr. M. K. Cook and colleagues (March 26, p. 905) is a reminder that most of the published observations on the prevalence of infection with Eaton's organism have been made within the United States. It may be of interest therefore to state that we have been able to demonstrate antibody to the same or an antigenically related organism in the sera of patients living in north-

eastern England and suffering from pneumonia or other respiratory illness accompanied by a raised serum titre of *Streptococcus MG* agglutinins. These observations have been made incidentally as part of a laboratory study of the properties of Eaton's organism.

The "Hetter" strain of Eaton's P.A.P. agent was used and propagated in the chick embryo. Frozen sections of infected chick embryo lung were prepared, treated with the sera from the patients, and subsequently with fluorescein-conjugated antihuman globulin. When these sections were examined in the ultra-violet light microscope characteristic fluorescence was seen in the area of the cells lining the smaller bronchi. Such fluorescence was not seen in control sections of uninfected chick embryo lung treated with the sera or in infected chick embryo lung sections which had not been treated with antiserum.

A specific rabbit antiserum to the "Mac" strain of Eaton's agent, kindly supplied by Dr. M. D. Eaton, also stained antigen in the same areas of infected chick embryo lung when tested by the fluorescent antibody technique. Lastly, it has been shown that a convalescent-phase serum taken from a local patient with "virus" pneumonia, and demonstrated to contain antibody against Eaton's agent by the fluorescent antibody method, would also prevent the formation of pneumonic lesions in hamsters infected with the organism by the intranasal route.—We are, etc.,

Public Health Laboratory Service, Leeds. B. P. MARMION.

Department of Bacteriology, University of Leeds. GILLIAN M. GOODBURN.

The Gas Man Cometh

SIR,—Dr. T. J. Crowley makes a very remarkable statement in his letter (March 12, p. 805): "A specialist qualification—even a low one—is unnecessary, nay superfluous," for the occasional anaesthetist.

Surely the price of safety is experience, and any general anaesthetic procedure involves a hazard which is increased by the inexperience of the administrator. Until such time as undergraduate teaching is improved in this specialty, it is little to ask that the conscientious practitioner who proposes to administer anaesthetics should prepare himself by a short course of training under supervision. On completion of training, which need only be six months, he can prove his competence by passing the D.A. examination, the demands of which are far from exhaustive. The examination only requires that the candidate is aware of the potential hazards of his techniques and will prove to be a safe anaesthetist.—I am, etc.,

St. Leonards-on-Sea, Sussex. VERNON R. KEEP.

High-pressure Salesmanship

SIR,—This morning's post brought me 31 communications, all unsolicited, from drug firms; one firm was responsible for eight, another with its offshoots for nine. Of the 31, two were addressed to one of my predecessors who left here in 1957, and four to my predecessors' predecessor, who left here in 1952; these people's present addresses are in the current *Medical Directory*. That leaves 25 addressed to me. Is this a record?—I am, etc.,

Westray, Orkney. JOHN PATTERSON.

Obituary

W. S. DICKIE, O.B.E., F.R.C.S.

Mr. W. S. Dickie, formerly honorary consulting surgeon to the West Riding Infirmary, Middlesbrough, died on March 20 at the age of 87. He had been living in retirement at Shipdham, Norfolk.

William Stewart Dickie was born in Glasgow on December 10, 1872. He began work as an office boy in an iron foundry at the age of 13, but by the time he was 15 he decided that the sea was his life and sailed as an apprentice in the four-master *Madagascar*. Having taken his second mate's certificate and later having passed his chief officer's examination, he set off in the *Kaffir Prince*, expecting to sit for his master's certificate on his return. In the interim, however, new eye-testing regulations came into force wherein no glasses were permitted in the test, which, as a consequence, he failed. The sea being thus cut off as a career, he resolved at the age of 22 to become a doctor. At Glasgow, where he studied medicine, he came in contact with Mr. J. Hogarth Pringle, who had a profound influence on his life, and there also he met a nurse, Jean Mitchell, who became his wife in 1902.

During his student days he gained the John Reid prize for his work on "The Structure of the Miliary Tubercle": this was so outstanding that the prize was awarded for two years. After serving as unqualified houseman to Sir David McVail, he qualified in 1900 and became house-surgeon to Mr. Hogarth Pringle. Later he went to Middlesbrough as assistant to Dr. Munro, but having taken the F.R.C.S. of England in 1903 he gave up general practice and was appointed surgeon to the North Riding Infirmary. In 1909 he built a small nursing-home, making provision for two additional stories later if required. He set himself the task of becoming a complete surgeon and travelled widely on the Continent for many years. Eventually, with his friend Pringle, he went to Canada and America, finishing up at the Mayo Clinic. As a result of meeting Lejars in France he undertook the translation of his *Chirurgie d'Urgence*, which in its English version ran through many editions.

Mr. Dickie served as a surgeon in the R.A.M.C. during the first world war and was appointed O.B.E. for his services. On returning to Middlesbrough he had to rebuild his nursing-home and added two more stories. In addition to his appointment at the North Riding Infirmary he was surgeon to the War Memorial Hospital, Whitby; Eston Cottage Hospital, Admiral Challoner Hospital, Guisborough; and the Rutson Hospital, Northallerton. A surgeon of international repute between the wars, he became a founder member of the Provincial Surgical Club of Great Britain and later its president. A Fellow of the Association of Surgeons of Great Britain, he was prominent at its discussions. His figure was tall and striking, and he never lost his Scottish burr. His contributions to surgery were the result of thoughtful evaluation of all the aspects of the problem under consideration and of the attention to intricate detail which characterized his operative procedures. The radical operation for cancer of the fauces which he evolved was typical of his refusal to accept inferior results. Beloved by his patients, he was always kind, gentle, and considerate, and many benefited from his great generosity. As a teacher of surgery he was unique, and Glasgow would have had another great teacher had he been able to remain there at the beginning of his career. He founded the Tees-side Clinical Club to bring the younger men of the profession together for discussion and for visits to teaching hospitals and academic centres. He lived for his profession, but, retaining a love of the sea, he delighted in sailing the boat which he kept on Loch Fyne.

After a serious operation in 1932 he resigned his position as honorary surgeon to the North Riding Infirmary but continued his other hospital appointments. Having retired from surgery in 1937, he acted as civilian adviser in surgery

to the hospitals in the north-east area during the early years of the last war, and later he took a keen interest in pistol shooting in the Home Guard. Eventually he went to live with his second son in Norfolk, where, after several years of failing health, his days were ended.

A member of the B.M.A. for nearly 60 years, he took a keen interest in its deliberations. He attended the Annual Meeting in 1906 as a representative of his Division and that in 1921 as secretary of the Section of Urology. Having been chairman of the Cleveland Division in 1922, he was president of the North of England Branch in 1926–7. He gave a chairman's chain of office to the Cleveland Division.

He leaves a widow, two daughters, and two sons. One son and one daughter are in the medical profession.—D. C. D.

J. C. NORMAN, M.B., B.S.

Dr. J. C. Norman, who formerly practised at Hebburn-on-Tyne, died at St. Mary's Hospital, Eastbourne, on March 1. He was 78 years of age.

John Charles Norman was born on April 6, 1881, and educated at Ushaw College, Durham, and at Durham University College of Medicine, where he graduated M.B., B.S. in 1905. Son of a doctor, brother of a doctor, and father of a doctor, he was very conscious and proud of his profession. He entered general practice at Hebburn-on-Tyne in partnership with his brother and in succession to his father, who had died a year or two previously. The family tradition is still carried on in the practice by his son and nephew.

During his 45 years of active practice he was much loved and respected by his patients, who referred to him only as "Dr. John." After retirement to Eastbourne in 1950 he had several happy years there. During his professional life he took an active interest in B.M.A. affairs, giving much thought to the various problems that arose. He resigned for a short while because of disagreement with policy, but when he saw that the Association had made a good case he rejoined in 1937. He was reluctant to assume office, and after previously refusing he eventually accepted the chairmanship of the South Shields Division in the year 1941–2. For many years he was a member of the Durham panel committee. A deeply religious man, he died after a long and painful illness.

He leaves a widow, a son, and a daughter, to whom we extend heartfelt sympathy and the assurance that his good work will long be remembered in Hebburn.—J. N. S.

R. ERRINGTON, C.B.E., *M.C.*, M.D.

Dr. Roger Errington, who had a distinguished record of military service in both world wars and was formerly attached as a medical officer to the Ministry of Pensions and National Insurance, died on March 14 after an operation. He was 72 years of age.

Roger Errington was born at Sunderland on October 26, 1887. He studied medicine at the College of Medicine, University of Durham, and graduated M.B., B.S. in 1911, proceeding M.D. in 1921. After holding several resident appointments at the Royal Victoria Infirmary, Newcastle upon Tyne, and at the Ingham Infirmary, South Shields, he joined the 1st Northumbrian Field Ambulance at the beginning of the first world war and served with it in France and Belgium until November, 1918. He gained the Military Cross and bar and was mentioned in dispatches. After the war he continued to serve in the Territorial Army and commanded his old field ambulance. He was appointed C.B.E. in January, 1939, and a few months later, when the second world war broke out, as a colonel in the Army Medical Services he went to France as A.D.M.S. of the Northumbrian (50th) Division. Evacuated from Dunkirk, he was later in command of military hospitals at Davyhulme, Manchester, and at Chester. He was again mentioned in dispatches (twice). From 1944 to 1949 he was Honorary Physician to King George VI. He was an Honorary Life Member of the British Red Cross Society.

Dr. Errington was never in general practice, but he worked for the Ministry of Pensions and National Insurance, of which he was a valued and respected member. He was a former president of the Newcastle upon Tyne and Northern Counties Medical Society. Conscientious, dependable, friendly, and with a keen sense of humour, he was an exceptionally fine man—a man of sterling qualities and of absolute integrity. His hobbies were golf, fishing, and shooting. He had many friends by whom he will be sadly missed. He was happily married and leaves a widow and son, to whom we extend our deep sympathy.—J. H. B.

D. L. SEWELL, M.B., B.S.

Mr. D. L. Sewell, consultant surgeon to the ear, nose, and throat department at Manchester Royal Infirmary, died at Chiddingfold, Sussex, on March 15. He was 81 years of age.

David Lindley Sewell was born on April 15, 1879, the son of a Manchester merchant. He received his medical education at Owens College and at Manchester Royal Infirmary. Qualifying in 1903, he graduated M.B., B.S., London, two years later. He had a brilliant academic career, gaining medals and distinctions all along the line, including the Bradley surgical scholarship and the junior and senior Robert Platt physiological exhibitions. His postgraduate studies were continued at Vienna, Würzburg, Munich, Heidelberg, Budapest, and Basle. In Manchester he worked in close association with the late F. H. Westmacott and the late Sir William Milligan. During the first world war he served in the R.A.M.C. in Mesopotamia and India. With his background and experience it was to be expected that he would join the staff of the teaching hospital in Manchester, and when a vacancy occurred in 1924 he was duly elected. He held this appointment until 1939, when he reached the retiring age of 60. He was the first laryngologist to the Christie Cancer Hospital and Holt Radium Institute when these two hospitals amalgamated and moved to their present site in 1932. Manchester University recognized his abilities as a teacher by appointing him clinical lecturer in diseases of the ear in 1922. When the B.M.A. held its Annual Meeting in Manchester in 1929 he was a vice-president of the Section of Otorhinolaryngology. On retiring from active practice he went to live at Troutbeck Bridge, near Windermere. A few years ago he left the Lake District and for a time lived in Devon, but within the last four years he moved again and spent his last years at Chiddingfold.

Mr. Sewell was a bachelor.

V. F. L. writes: Mr. Sewell was a very competent surgeon, even if conservative in his approach and perhaps a little restricted in his surgical world according to present standards. The quality of his work in temporal-bone and nasal surgery would stand comparison with any standards. His most outstanding contribution to the progress of his specialty in Manchester was the introduction of Chevalier Jackson's instruments and technique in the art of peroral endoscopy. He was one of the earliest and best exponents of the Finzi–Harmer operation.

As a man, Sewell was widely read and the possessor of a cultured mind. He loved outdoor pursuits, being devoted to fishing and shooting, and for many years was a regular visitor to the ski slopes of Lenzerheide. He was an entertaining and interesting companion with a puckish sense of humour, but with his strong character he was unshakable in any line of action which he had determined to follow. This is well illustrated by an incident occurring in Mesopotamia during the first world war, when he was ordered by his colonel to remove the tonsils of 30 "other ranks" because they were alleged to be carriers of the diphtheria bacillus. Disapproving wholeheartedly of this method of approach, and also of operating under existing

conditions except in real urgency, he refused to carry out the order despite the threat of a court martial—adding more coals to the fire by telling the colonel to do the operations himself.

W. ELDER, M.D., D.P.H.

Dr. W. Elder, of Annan, Dumfriesshire, died on February 24 at the age of 81.

William Elder belonged to Glasgow and graduated in medicine at the university there in 1901. He held the appointments of house-surgeon and house-physician at Glasgow Royal Infirmary, and shortly afterwards served as a civil surgeon during the South African war. When he returned home he went into general practice at Annan, where he worked on his own until shortly after the end of the second world war, when he was joined in partnership by his eldest son.

R. L. B. writes: With the death of Dr. W. Elder, of Annan, the Dumfries and Galloway Division of the B.M.A. has lost its senior member. He served the community for over fifty years and held a multitude of local offices. He had his full share of misfortune, for he lost an eye early in his career in a laboratory accident, his wife died in 1931 after only ten years of marriage, and his younger son, a pilot in the Fleet Air Arm, was shot down in action over Norway in April, 1945.

He was ever a man of action—a clear thinker and a good committee-man. Devoting a great deal of his time to the Dumfriesshire panel committee, he was for many years its very active secretary. A long-standing member of the executive committee of the Dumfries and Galloway Division of the B.M.A., he was chairman of the Division in 1932 as a general practitioner. One of his special interests was the Red Cross, and he was awarded the Red Cross medal for his work for this organization. His outside interests in golf, cars, and bowling were never allowed to interfere with his work, for he was first and foremost a general practitioner of the old school, and, as his patients well knew, his gruff exterior was only a cloak for a very warm-hearted personality. His candid criticism was freely voiced in public, as well as in private, on many subjects, including over-prescribing. The efficiency of the hospital service in Dumfries and Galloway owes much to his stimulus.

"Wee Elder," as his colleagues knew him, will be much missed in Annandale. This aggressive-looking little man, with his eye-shield and his hurrying gait, was a kenspeckle figure, feared yet beloved of all. He never really retired (though he had not worked for the past two years), but preserved his interest in his patients, the Stock Exchange, and television to the end of the chapter, which closed quietly on February 24.

C. M. RIGBY, M.R.C.S., L.R.C.P., D.M.R.E.

Dr. C. M. Rigby, formerly a regular officer in the R.A.M.C. and, later, radiologist to the Royal Hospital, Wolverhampton, died at his home at Middleton-on-Sea, Sussex, on January 28. He was 78 years of age.

Claude Mallinson Rigby was born in Dublin in 1882. Educated at Dulwich College and the London Hospital, he qualified in 1907. In the following year he joined the R.A.M.C. and served in it with distinction. From 1915 to 1918 he was surgeon to the Governor of Bombay, then Lord Willingdon, and from 1921 to 1923 he was surgeon to Lord Rawlinson when he was Commander-in-Chief, India. On returning to England he entered the specialty of radiology, taking the D.M.R.E. while still a serving officer, and for a time he was radiologist at the Cambridge Military Hospital, Aldershot, to which he returned in 1940 when he was recalled into the R.A.M.C. during the second world war.

He retired from military service as a major in 1928, and entered the civilian practice of radiology in Wolverhampton in 1929. He held honorary appointments at the Royal Hospital, Wolverhampton, the Guest Hospital, Dudley, the Corbett Hospital, Stourbridge, and at the General Infirmary, Stafford, until his retirement in 1947.

Claude Rigby was a man of great personal charm and modesty, which endeared him to all who knew him. He was a fine athlete, playing rugger for the London Hospital as a student, and was also a good tennis-player. A keen and consistent golfer, he was a member of the R.A.M.C. Golfing Society and of the South Staffordshire Golf Club, where he enjoyed a great popularity.

As a radiologist he served the Midlands with distinction and helped to build the radiological services in that area. Perhaps his modesty forbade the full recognition of the great amount of unassuming work which he did.

Claude Rigby married Mary Elaine Booth in 1920, and she survives him together with a daughter of the marriage.

SIDNEY BRÉE, M.B.

Dr. Sidney Brée, who retired from general practice at Manningtree, Essex, in 1939, died at his home at Felpham, near Bognor Regis, on February 23. He was 83 years of age.

Sidney Brée came of a very old Jersey family, and was educated at the Victoria College, Jersey, and at University College, London. He qualified in 1900 and graduated M.B. in the following year. Having been house-surgeon to Sir Rickman Godlee at U.C.H., he held an obstetric appointment in Bethnal Green before deciding to enter general practice. He saw service in the first world war in Salonika and in France, and, though he had retired from practice before the second world war, he took a very active part in training civil-defence workers at Bognor Regis. He was always interested in first-aid work, and had founded the Manningtree division of the St. John Ambulance Brigade soon after he took up practice there. Subsequently he became assistant commissioner for the county of Essex and an Officer of the Order of St. John of Jerusalem. He was much loved in Manningtree and the surrounding country, where he is still remembered with affection as a family doctor in the best tradition.

He leaves a widow, a son who is in general practice in Norfolk, and a daughter whose husband carries on his old practice with the help of his grandson, to all of whom our deep sympathy is extended.—W. R.

J. F. CARTWRIGHT, M.R.C.S., L.R.C.P.

Dr. J. F. Cartwright, senior medical officer to Sir W. G. Armstrong Whitworth Aircraft Ltd., died suddenly at his home at Leamington on March 2. He was 47.

John Fraser Cartwright was born on September 27, 1912. Educated at Bedford Modern School, Emmanuel College, Cambridge, and St. Bartholomew's Hospital, he qualified in 1940. After house appointments in medicine and surgery at Bart's he served in the Royal Air Force, but was invalided out in 1943 and entered industrial medicine the following year, remaining in the same appointment until his death.

B. C. writes: The death of John Cartwright was entirely unexpected and is a great loss to industrial medicine. He was a most lovable person, unassuming, thoughtful, and considerate in every way. He applied great enthusiasm and painstaking care to his work and was a very competent medical officer. An authority on aviation medicine, he was engaged in intensive research during the last few years of his life on the occupational hazards associated with beryllium and guided missiles. He combined a deep knowledge of industrial psychology with a kindly understanding of the industrial worker and his problems. He will be sadly missed not only by his medical and managerial colleagues but by every employee in the A.W.A. group of factories, for he endeared himself to all by his unselfish and unfailing consideration for others.

He leaves a widow and two daughters, and all in the Midlands who knew John Cartwright extend to them their heartfelt sympathy in their tragic loss.

G. A. ANDERSON, M.R.C.S., L.R.C.P.

Dr. G. A. Anderson, who practised in Sheffield, died on March 5, aged 46.

George Alexander Anderson, the son of the late Dr. C. M. Anderson, was born in Sheffield on April 4, 1913. He was educated at King Edward VII School, Sheffield, where he won his colours for football and cricket. His medical studies began at the Sheffield University and were completed at Durham. Qualifying in 1941, he served during the second world war as a surgeon-lieutenant in the Royal Navy. On demobilization he went into general practice in Sheffield, being a member of a family partnership of five. He also served on the military recruitment and pensions boards. An enthusiastic golfer, he had been captain of his club.

W. W. M. writes: Dr. G. A. Anderson had a most genial and charming personality which endeared him to his patients. Unfortunately four years ago he fell a victim to leukaemia. Throughout his illness his courage never failed, and he kept working cheerfully to within a fortnight of his death. Many were the letters from patients expressing their admiration of his exemplary fortitude.

F. J. JACK, L.R.C.P.&S.Ed.

Dr. F. J. Jack, who practised at Ellesmere Port, Cheshire, died in hospital on March 11, aged 69.

Frederick Joseph Jack was born in Fifeshire on April 20, 1890. Qualifying at Edinburgh in 1916, during the first world war he served with the 4th Battalion, King's African Rifles, for three years in British East Africa, and remained in the R.A.M.C. until 1920. He was house-physician at Salford Royal Infirmary in 1921 and then entered general practice in Manchester, where he stayed for eight years. In 1929 he went to Ellesmere Port and remained there until his death. During this latter period he was medical officer to Bowaters' Paper Mills, a post which he held from its inception. He was also medical officer to the Manchester Ship Canal Company. A past president of the Chester and North Wales Medical Society, he was an original member of the Ellesmere Port and District medical committee.

Fred Jack was a most popular figure, liked equally by his colleagues and his patients. A person of the utmost integrity, he upheld by his example the ethics of his profession to the highest degree. His counsel and foresight will be greatly missed in the social life of the community.

HENRY GRANGER, M.R.C.S., L.R.C.P.

Dr. Henry Granger, honorary consulting physician to the ear, nose, and throat department of the Royal Victoria and West Hants Hospital, Bournemouth, died on March 14 at his home in Bournemouth at the age of 78.

Henry Granger was born at Wimbledon on June 2, 1882, and educated at King's College School, Wimbledon, and St. Thomas's Hospital, qualifying in 1907. His entire medical career was spent in Bournemouth, except for his service during the first world war, for he held the post of house-surgeon at the Royal Victoria Hospital from 1908 to 1912. On relinquishing this appointment he joined Dr. Muspratt and Dr. Simmons in their general practice, paying special attention to the diseases of the ear, nose, and throat. In 1913 he was appointed assistant surgeon to the ear, nose, and throat department at the hospital. This appointment, and later that of honorary physician, he held for thirty-five years and he was then made honorary consulting physician. He was also assistant police surgeon in Bournemouth for many years. A member of many committees serving the interests of the hospitals and the National Health Insurance service, he held among other offices the post of president of the Bournemouth Medical Society, of which he had been a member for forty-eight years. Outside his practice, his chief interests were horse-racing and shooting, which he was able to enjoy until a few years ago.

His lovable character endeared him to his many colleagues, patients, and friends, as was evidenced by the large attendance at his funeral at St. Peter's Church. He leaves a widow, two sons, and a daughter, to whom our sympathy is extended.—E. B.

Medical Notes in Parliament

POLIO VACCINATION PROGRAMME

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Mr. L. PAVITT (Willesden, West, Lab.) renewed in an adjournment debate on March 30 his criticisms of the way the extension of the poliomyelitis vaccination service was made known in February. This extension to all citizens up to the age of 40, he said, was generally welcomed. But the Minister's announcement of it on February 1 in the House* left the impression that it would be immediately available. In Willesden the area medical officer received his first intimation that it was proposed there should be an extension on February 4, and it was not until February 24 that the memorandum was issued by the county medical officer to his local area officers saying that the county council had decided to implement the scheme and that it was in order to go ahead. In the meantime each area medical officer had been inundated with requests from general practitioners, and factory staffs had begun to worry the area officer of health. All this caused unnecessary work and frustration locally and administrative difficulties that ought not to have occurred.

Repeated Ministry Mishandling

More important than the harm done to relations with the public was the loss of good will between the Ministry and the medical profession. Were this an isolated case of the Ministry mishandling its relations with the profession his questioning of the Minister earlier this month might have settled the matter. But from the outset the arrangements for polio vaccination had caused difficulties with the profession. He quoted a leading article from the *British Medical Journal* of January 28, 1956, headed "Another Ministry Blunder," and saying "... we were most unfortunately kept completely ignorant of the details of the Ministry of Health's scheme and so were not in a position to give them to our readers," and others in April and October that year.†

He had two other points of criticism. He understood that doctors had given some 30 million injections. It was a remarkable achievement, but in fact payment was all deducted from their pay at the end of the year. It was taken out of the Central Pool, and they did this extra service for no additional payment. Secondly, because of the arrangement, the doctor who sent in the form got paid, but not necessarily the doctor who made the jab.

Programme a Matter of Major Public Interest

Miss EDITH PITT, Parliamentary Secretary to the Ministry of Health, maintained that extensions to the poliomyelitis vaccination programme were of major public interest and importance, and that the House should be informed directly and as soon as possible of impending major variations. On recent occasions the first announcement of extensions to the programme had therefore been made in answer to Parliamentary questions, and had received wide publicity. The first announcement that vaccination would be available was made by press notice at the same time as the circular was sent to local health authorities on January 19, 1956.

*See *Brit. med. J.*, February 6, p. 436.
†*Brit. med. J.*, 1956, **1**, 220 and 850; **2**, 929.

Consultations with local-authority associations and the B.M.A. were carried out confidentially in advance of the public announcement, so that synchronization was easy.

The first extension in May, 1957, was announced by the Minister in the House on May 15, the day after a circular had been sent to local authorities; again consultation with local-authority associations and the B.M.A. had been carried out confidentially in advance. When the second extension was made in November, 1957, public interest in the programme, combined with apprehension about the supply position, was at such a pitch that it was thought desirable for an encouraging statement to be made publicly at the earliest possible moment. The press notice was therefore issued on September 11 that the extension would be made "before the summer of 1958." Consultations with local-authority associations and the B.M.A. were then needed before the circulars could be issued on November 19, well in advance of the time. The third extension was forecast in a Parliamentary answer by the Minister on July 21, 1958, when he said it was hoped to make a start by the autumn—again because public interest was at a high pitch. Consultations were then needed, and the circular was issued on September 2. The fourth extension was announced on February 1, and at the same time a circular was sent to local health authorities. As public interest was not at such a high pitch, and advance notice of making the extension had been given in the Conservative Party election manifesto, it was again possible for consultations to be carried out confidentially before the public announcement was made, so the announcement and the circulars could be simultaneous.

In general, and ideally, no public announcement would be made until final preparations for giving vaccination were completed. They had succeeded, save on the two special occasions mentioned, in eliminating the interval between public announcement and the issuing of circulars to local health authorities and executive councils by completing consultations with the associations beforehand. The remaining interval between the issue of circulars and a state of readiness in clinics and surgeries could not be eliminated, because it was impracticable to release instructions confidentially to 146 local authorities and thousands of individual doctors.

The Government saw considerable advantage from a publicity point of view in making the first announcement of changes a central, national one, through Parliament and the press.

Fee for Vaccination Records

On the fee paid, it was agreed in 1949 between local health authorities and the B.M.A. that the fee for vaccination records should be 5s. Since doctors were paid on an average figure, estimated to cover net remuneration from all sources, it followed that any net income they received from other sources—such as hospitals, local authorities, other Government departments, and private practice—had to be deducted from the Central Pool.

Miss PITT concluded with a tribute to those on whom the main burden of vaccination had fallen. By the end of 1959 about 33 million injections had been given, a tremendous achievement in such a short time. The summer of 1959 was one of the warmest and sunniest of the century. Previous experience suggested that in such summers polio figures tended to go high. One hesitated to claim too much credit for vaccination. But since 1947 there had been both bad years and relatively good years. It was noteworthy that 1958, when vaccination was well under way, should have been one of the good years; and that 1959, by which year three out of four children under 15 had received at least two doses, should have been even better.

QUESTIONS IN THE COMMONS

W.H.O. Malaria Fund

Mr. PAVITT asked the Minister of Health on March 28 what reply was given by the Government to W.H.O.'s request for a contribution to its special malaria eradication fund. Mr. WALKER-SMITH said the Government regretted that they did not feel able to make any further contribution to malaria eradication work additional to that which they already made by way of their contributions to the regular budgets of W.H.O. and to the United Nations Children's Fund and the expanded programme of technical assistance, as well as by way of the antimalaria work undertaken in Her Majesty's territories overseas.

Mr. PAVITT also asked the Minister if he would propose at the next meeting of W.H.O. that all member-States be asked to increase their contributions to the organization in order to enable it to meet the cost of a special campaign to eradicate malaria. Mr. WALKER-SMITH replied "No." He did not think that it would be appropriate to put forward such a proposal. The United Kingdom, he explained, had substantially increased its contribution over the years to the W.H.O. budget. We were the third largest contributor to it. That budget had itself doubled over the past six years, and there had been a further increase of nearly 10% in 1961.

Oral Contraceptives

Miss JOAN VICKERS (Plymouth, Devonport, Con.) asked the Minister on March 31 whether he would refer to the Medical Research Council the claims made for oral contraceptives, and arrange for the Council to conduct tests with adequate safeguards against undue risks to volunteers from side- or long-term effects. Mr. WALKER-SMITH: I do not think this is necessary. I am informed that the Medical Research Council have this whole subject very much in mind, and have for long been sponsoring fundamental research into the factors affecting human fertility and infertility.

Medico-Legal

LADY HOARE AND THE LONDON CLINIC

[FROM OUR LEGAL CORRESPONDENT]

On March 24 the House of Lords delivered judgment in the case of the London Clinic Ltd. Trustees *v.* Hoare (*The Times*, March 25). Their Lordships, reversing the decision of the Court of Appeal (*Brit. med. J.*, 1959, **1**, 1483), held that the London Clinic was entitled to £73, being the balance of fees outstanding for the treatment of the late Sir Reginald Hoare, which Lady Hoare refused to pay.

Lady Hoare based her refusal to pay on her allegation that the London Clinic had been negligent in the nursing services they had provided, and had thereby shortened her husband's life. It was found at first instance, and the appellate courts agreed, that nothing done or omitted by the clinic had in any way accelerated Sir Reginald's death. The Court of Appeal held, however, that the clinic had contracted to provide a very high standard of nursing and care, had fallen short of this standard in a material degree, had thereby broken the contract, and in the circumstances the £73 outstanding was not payable, as it represented the difference in value between the contract as it ought to have been performed and the contract as it was in fact performed.

Although it was not clearly stated by the Court of Appeal, the House of Lords regarded that court's decision as being based on a set-off of damages for breach of warranty in some respect not pleaded by Lady Hoare. No court has jurisdiction simply to reprice a contract upon hearing evidence of the quality of performance: the only related jurisdiction is to set off damages found to be due on the proven breach of some warranty. It was the view of the House of Lords that only one of the breaches alleged by Lady Hoare amounted to carelessness or lack of skilled service on the part of the clinic: that was the matter concerning the "pitressin" prescription, referred to in our earlier report. This matter, however, had had no injurious effect on Sir Reginald at all. When a nursing-home

contracted to provide accommodation and attendance, it did not warrant that its organization would never make a mistake or would never fall below the highest standards. So long as such mistakes or failings, if any, did not prejudicially affect the patient, he got what he contracted for and had no right to damages.

NEW TRIAL FOR HYPNOTIST

[FROM OUR LEGAL CORRESPONDENT]

Victor Vinmar, of Upper Fitzwilliam Street, Dublin, the hypnotist who was described by the judge as a fraud in a county court action which he failed to defend (*Brit. med. J.*, March 12, p. 813), has successfully applied to the Coventry County Court for a new trial (*Birmingham Post*, March 22). Leave was granted on condition of payment into court of the sum in issue and the sum in respect of costs. The plaintiff patient was entitled to the costs of the first hearing in any event. Mr. Vinmar stated that his real name was George Joseph Cassidy, of Upper Fitzwilliam Street, Dublin, but that he had not appeared at the original hearing because he had anticipated a settlement out of court. He wished now to defend his good name.

CORONERS' CASES

Sudden Death on March

The sudden death of a fit young National Service man was the subject of an inquest at Catterick Camp on March 4. Signalman Robert Henry Peacock, aged 20, was on a routine march and had covered four-and-a-half miles at a normal pace, without equipment, when he collapsed and died within a few minutes. He had not previously complained of feeling unwell. A post-mortem examination revealed the presence of virus pneumonia, and this was stated to be a known cause of sudden death with minimum symptoms. The pathologist said, "The route march would not have done him any good in his condition, but he might have died just the same if he had been in a classroom." Recording a verdict that death was due to natural causes, the coroner, Mr. P. Hatch, said, "There is no suggestion that anyone, including Peacock himself, could have known the serious condition he was in when he set out on the march." (*Yorkshire Post*, March 5.)

An Inadequate Message

The husband of a patient who took her life while the balance of her mind was disturbed protested at a Newton Abbot inquest that the doctor had failed to visit promptly after a telephone call and a personal request. The deceased, aged 54, had a long history of rheumatoid arthritis. She had an operation in December from which she made a good recovery. The night before she died she had been in pain and was vomiting. The doctor was called by phone at 8.35 a.m., and later a relative called at the surgery and was told that the message had been received. It was not made clear to the doctor that an immediate visit was required. When he called later in the morning the patient had gassed herself.

Recording the verdict, the coroner, Mr. John Hutchings, said that the deceased had left a letter plainly stating her intention of taking her life because of the pain she was suffering. He went on: "I can understand that the relatives may feel, perhaps strongly, that medical attention should have come earlier, but it does appear that the facts really are that the doctor was not asked to go immediately and did so in the course of his rounds. One must realize that unless a degree of urgency is stressed a doctor who has to attend other people may be left to think that this is something which can await his attention during his normal duties." The fact that the deceased had been able to sit and write letters during the morning, added the coroner, rather confirmed the view that perhaps her condition at that time was not dangerous from the medical point of view. (*Western Morning News*, March 11.)

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 19** (No. 11) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	2	0	1	3	0	1	0	1
Dysentery	1,874	192	236	32	7	1,171	133	136	14	
Encephalitis, acute	4	0	0	0		1	0		0	
Enteric fever:										
Typhoid	1	0	0	0		0	0	0	0	
Paratyphoid	1	0	0	0	2	9	2	0	0	
Food-poisoning	174	24	7	0		131	9	9	2	
Infective enteritis or diarrhoea under 2 years				12	21				14	18
Measles*	2,247	100	64	6	90	22,338	1262	1136	510	666
Meningococcal infection	23	2	9	0		30	3	6	2	
Ophthalmia neonatorum	31	4	6	0		29	8	0	0	
Pneumonia†	414	19	210	9	2	1,452	58	369	15	13
Poliomyelitis, acute:										
Paralytic	4	0	0	} 0		{ 8	2	1	} 0	
Non-paralytic	4	0	0			3	1	0		
Puerperal fever§	166	19	11	0		197	33	7	3	
Scarlet fever	1,176	50	82	24	12	1,084	53	66	22	13
Tuberculosis:										
Respiratory	469	59	68	16		647	58	95	14	
Non-respiratory	69	6	6	3		59	4	9	1	
Whooping-cough	896	72	193	3	30	533	17	55	42	125

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		2	0	0	0	
Infective enteritis or diarrhoea under 2 years	9	0	2	0	0	5	0	0	0	
Influenza	33	0	0	0	1	590	16	17	3	17
Measles	0	0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0	0	0
Pneumonia	734	63	14	17	7	1,058	75	40	36	16
Poliomyelitis, acute	1	0		0	0	2	0		0	0
Scarlet fever	0	0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	} 75	{ 4	9	0	5	} 102	{ 13	10	0	3
Non-respiratory		2	0	1	0		1	1	0	1
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	347	29	32	10	9	319	38	42	7	13
Deaths (excluding stillbirths)	11,242	864	603	140	170	11,985	868	753	167	228
LIVE BIRTHS	16,115	1366	1031	216	371	15,766	1341	1120	257	322
STILLBIRTHS	333	33	23			322	26	27		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Mar. 19	Week Ending Mar. 26
Measles		
Devonshire	129	**116**
Exeter C.B.	87	**77**
Dorsetshire	136	**132**
Poole M.B.	26	**46**
Sturminster R.D.	65	**48**
Hampshire	95	**125**
Christchurch M.B.	59	**59**
Kent	229	**221**
Ashford U.D.	166	**136**
Lancashire	634	**549**
Liverpool C.B.	147	**137**
Eccles M.B.	128	**92**
Dysentery		
Cheshire	55	**115**
Bollington U.D.	8	**45**
Stalybridge M.B.	17	**25**
Essex	67	**89**
Romford M.B.	19	**24**
Gloucestershire	58	**52**
Bristol C.B.	33	**43**
Kent	42	**101**
Chatham M.B.	4	**23**
Deal M.B.	12	**16**
Sevenoaks R.D.	1	**18**
Lancashire	409	**470**
Manchester C.B.	6	**23**
Preston C.B.	32	**17**
Lancaster M.B.	0	**17**
London	192	**257**
Islington	20	**37**
Southwark	49	**47**
Wandsworth	18	**30**
Nottinghamshire	60	**85**
Carlton U.D.	8	**14**
Bingham R.D.	24	**40**
Yorkshire West Riding	213	**240**
Bradford C.B.	36	**50**
Leeds C.B.	53	**50**
Sheffield C.B.	58	**50**
Heckmondwike U.D.	2	**20**
Glasgow	108	**102**
Edinburgh	20	**36**
Food-poisoning		
Surrey	0	**37**
Woking U.D.	0	**37**

Deaths in 1958

A report published this week gives details about causes of death and illness in England and Wales during 1958. The perinatal mortality rate (deaths under one week plus stillbirths per 1,000 total live and stillbirths) was 35: the rate was highest in Wales (41) and in the north-west (40) and lowest in eastern and southern England (30).

The deaths from cancer were over 18% of all deaths, and were 1,787 more than in 1957. Deaths from cancer of the lung (up by 701 over the previous year) accounted for 33% of the male and for 6% of the female deaths from cancer. For males the death rate from cancer of this site has risen from 65 per 100,000 of the population in 1954 to 78 in 1958 (and for females from 10 to 12). If the experience of the United Kingdom as a whole is taken as 100, the ratio for deaths from cancer of the lung in England and Wales was 100 for males and 99 for females; for Scotland, 106 for males and 116 for females; for Northern Ireland, 58 for males and 72 for females.

Sixteen per cent. of all deaths were due to coronary heart disease. The rates have increased since 1954 from 202 to 240 for men and from 108 to 137 for women.

So far as deaths from infectious diseases were concerned, there were 8 deaths from diphtheria (compared with 4 in 1957 and 3 in 1956). Deaths from scarlet fever and whooping-cough numbered 4 and 27 (both record low figures).

Accidental deaths in the home or residential institutions caused by domestic gas totalled 832 (110 more than in 1957); 539 of these persons were aged 65 or over. Over two-thirds of the accidental deaths (total, 10,405), other than traffic accidents, occurred in the home or in residential institutions, and of these just over 60% (4,287 out of 7,001) were due to falls. Over two-thirds of all fatal accidental falls were in people aged 75 or over.—*The Registrar-General's Statistical Review of England and Wales for the Year 1958.* Part I, Tables, Medical, 1960, H.M.S.O., London. Price 20s. net.

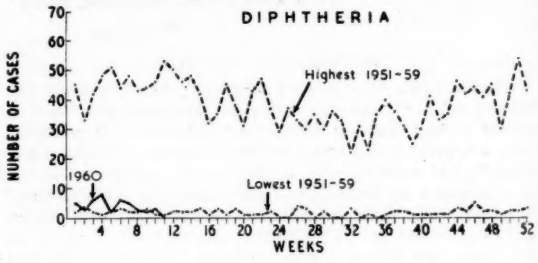
Industrial Accidents and Diseases

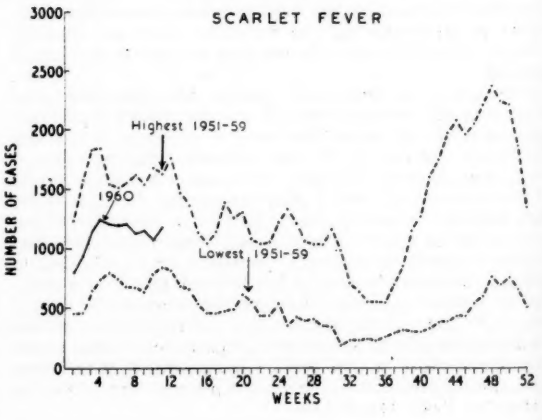
The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in February was 88, compared with 72 in the previous month and 108 in February, 1959.

The numbers of cases of industrial diseases in the United Kingdom reported during February were as follows: lead poisoning 9, toxic jaundice 1, epitheliomatous ulceration 7, chrome ulceration 11; total 28. There were no deaths.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ————. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





Medical News

Oral Contraceptives

About 40 women, half in Devon and half in London, are at present the subjects of a trial of oral contraceptives, and it is hoped to extend the trial now to 100 volunteers in Birmingham. This information was given at a press conference held in London last week under the auspices of the International Planned Parenthood Federation, with Dr. C. P. BLACKER in the chair. Dr. A. S. PARKES, F.R.S., convener of the research committee of the I.P.P.F., explained that the present methods interfered with the hormonal mechanism causing ovulation. The ovum was released in response to a hormone secreted by the anterior pituitary. Administration of a progestogen apparently overwhelmed the pituitary and prevented this, but just how it happened was not entirely clear. Dr. ELEANOR MEARS, medical secretary of the Family Planning Association said that the results reported from the U.S.A. by Pincus showed that this method seemed to be harmless so far. It was not carcinogenic, did not affect a woman's ultimate fertility, and did not postpone the menopause. Side-effects were headache, gastro-intestinal upsets, and irregularities in menstrual bleeding. They stopped when the pills were withdrawn. Smaller doses were being tried in order to cut down side-effects. Dr. MARGARET JACKSON, convener of the evaluation committee of the I.P.P.F., said the substances being used were norethynodrel (" enavid ") and norethindrone (" primolut N "). In addition a few women were receiving dimethisterone (" secrosteron "), but she did not think it would be effective for this purpose. Dr. Jackson mentioned that a substance causing infertility in male rats was the subject of experiments by Dr. H. Jackson, of Manchester. [H. Jackson, B. W. Fox, and A. W. Craig, *Brit. J. Pharmacol.*, 1959, **14**, 149, have reported on the interference with spermatogenesis in rats by cytotoxic alkylating agents such as tretamine and busulphan.] Dr. Parkes added that oestrogenic substances tried in the U.S.A. on men had caused impotence. Dr. Mears and Dr. Parkes made the point that, if a woman who was infertile from lack of natural progestogen took the contraceptive pills for part of the cycle, and accidentally omitted them for part of it, her fertility might be increased.

Rheumatism in Industry

The Empire Rheumatism Council is to finance a survey of British industry to investigate—among other problems—the incidence of rheumatic conditions among the working population and to discover how much disability and loss of time can be attributed to them. The effect of certain occupations on rheumatic complaints will also be studied. The survey will be directed by Dr. J. J. R. DUTHIE, senior lecturer, department of medicine, Edinburgh University, who has said that more than 730,000 persons employed in Britain claim sickness benefit each year because of rheumatism—this represents an annual loss of more than 27 million working days.

Chair of Anatomy, Durham University

Dr. R. J. SCOTHORNE, senior lecturer in anatomy at Glasgow University, has been appointed to the chair of anatomy at King's College, University of Durham, from October 1.

He took his B.Sc. at Leeds University in 1941, and then held from 1941 to 1943 a Rockefeller Studentship in Medicine at the University of Chicago, becoming M.D. Chicago in 1943. He passed M.B., Ch.B. at Leeds in 1944, proceeding to M.D. (distinction) in 1951. He was demonstrator in anatomy at Leeds from 1944 to 1945 and lecturer in the subject from 1945 to 1950. He then took up his present position at the University of Glasgow. Dr. Scothorne has published papers on the comparative embryology of the thyroid, parathyroid, and thymus, on histological aspects of skin homotransplants, and on salt and water balance in birds.

Royal Society Tercentenary and B.B.C. T.V.

During April and May B.B.C. television will mark the Royal Society's tercentenary celebrations with a series of scientific programmes showing the current research work of some of the Society's Fellows.

The medical programmes in this series will show something of Dr. C. H. ANDREWES's work on influenza and the common cold; Sir FRANK MACFARLANE BURNET's on immunology and the production of antibodies; Professor J. MCMICHAEL's on the pulmonary circulation of the blood; Dr. M. F. PERUTZ's and Dr. J. KENDREW's on the structure of protein; and Dr. WILDER PENFIELD's on neurology.

Medical Censorship on Sound and T.V. in Australia

In Australia the censorship of broadcast medical talks and advertisements relating to medicine has been a duty of the Commonwealth Department of Health since the Broadcasting Act, 1942–54, and this duty of censorship was extended to television on July 1, 1956. A brief résumé giving these facts is contained in the Commonwealth of Australia's *Report of the Director-General of Health, July 1, 1956–June 30, 1958.* No details are given of the principles on which decisions in such matters are based, or the frequency with which the Department's right of veto is invoked.

Casualty and Out-patients, Northampton General

The new £400,000 casualty and out-patients department at Northampton General Hospital—first conceived in 1945 as a memorial to the people of the district killed during the second world war—has recently come into full use.

The new unit, which is on a steeply sloping site, is at the extreme southern edge of the existing hospital and is connected

[*F. Jewell-Harrison*

to it by an underground service duct and by a covered way above ground. The main entrance area leads into the foyer, shown here, where the out-patients can find a reception counter, snack bar, transport office, and pharmacy. The three-story building includes 30 beds for accident cases, two operating-theatre suites, radiography rooms, a pathological laboratory, an isotopes room, a dental department, and hearing-aid and audiometry rooms. There are a number of special services, such as an emergency lighting system, piped supplies of sterile water throughout the building, and, in some areas, piped oxygen, nitrous oxide, vacuum, and compressed air. All departments have a main supply of steam for sterilizers, and the theatre unit and the sterile-products room are mechanically ventilated.

Cancer and the Public

The Central Council for Health Education has set up an advisory committee on cancer education which will correlate activities, act as a clearing-house for information, provide a forum for discussion, and will organize conferences and other activities. This committee will work from the office of the Central Council for Health Education, Tavistock House North, Tavistock Square, London, W.C.1, and those who are interested are invited to write to the Medical Director.

Membership includes representatives of the following organizations: The Central Council for Health Education, Cancer Information Association, Marie Curie Memorial Foundation,

Manchester Committee on Cancer Educational Project, British Medical Association, College of General Practitioners, Society of Medical Officers of Health, Royal College of Nursing, Queen's Institute of District Nursing, Royal Society of Health, Royal College of Midwives, and the Postgraduate Medical School of London, with observers from the Ministry of Health and the Ministry of Education.

Carlsberg-Wellcome Travelling Research Fellowships

Applications—to be submitted before April 30—are invited for the Carlsberg-Wellcome Travelling Research Fellowships, 1960–1, the object of which is to encourage co-operation, on an exchange basis, between Danish and British research workers in any branch of the natural sciences which has a bearing upon human and animal medicine. Details may be obtained from the Assistant Scientific Secretary of the Wellcome Trust, 52, Queen Anne Street, London, W.1.

One Fellowship annually is awarded to a candidate from the United Kingdom for a year's work in Denmark and one annually to a Danish candidate for a year's work in the United Kingdom. The stipend may range from £900 to £1,300 a year, travelling and some incidental expenses being provided in addition. The tenure of the awards will start in September, 1960.

COMING EVENTS

National Society for Mentally Handicapped Children.—Annual convention, April 9, 2.30 p.m. to 4.30 p.m., Friends House (Great Hall), Euston Road, London, N.W.1.

"Eye on Research."—Dr. C. H. ANDREWES, F.R.S.: "Influenza and the Common Cold," B.B.C. T.V.: April 12, 10 p.m.

Institute of Diseases of Chest.—Clinical demonstrations, open to medical practitioners without fee, will be arranged by Dr. J. L. LIVINGSTONE in the Institute's lecture room (in Brompton Hospital grounds, Fulham Road, S.W.3) on Fridays at 5 p.m., April 22 to July 8.

Naval Medical Compassionate Fund.—A meeting of the subscribers to elect six directors will be held at 2.45 p.m., May 13, Medical Department of the Navy, Queen Anne's Mansions, St. James's Park, London, S.W.1.

St. Stephen's Hospital.—Week-end course on "The Chronic Rheumatic Diseases," with lectures, ward rounds, and practical demonstrations, Rheumatism Unit, St. Stephen's Hospital, Fulham Road, Chelsea, London, S.W.10, May 14 and 15. Details from the Secretary, Fellowship of Postgraduate Medicine, 60, Portland Place, London, W.1.

6th Congress of Scandinavian Society of Anaesthesiologists.—University Hospital, Gothenburg, Sweden, June 30–July 2. Details from N.A.F. Congress Office, P.O. Box 45, Hovas, Sweden.

26th International Congress on Alcohol and Alcoholism.—Stockholm, July 31–August 5. There will be five main themes: (1) alcohol consumption and legislation in different countries; (2) alcohol problems in industry and road traffic; (3) treatment; (4) education and prevention; (5) results of medical and sociological research (in co-operation with the Committee for Alcohol Research of the Swedish Medical Research Council). Details from 26th International Congress on Alcohol and Alcoholism, Box 5071, Stockholm 5, Sweden.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

*The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.*1.

BRITISH JOURNAL OF OPHTHALMOLOGY.—Issued monthly (£6 annually). The new issue (Vol. 44, No. 3) includes:

Larval Granulomatosis of the Retina due to *Toxocara*. N. Ashton.
Impression Tonometry and the Effect of Eye Volume Variation. C. I. Phillips and M. C. Quick.
Incidence and Causes of Blindness in the Maltese Islands. F. J. Damato.
Association between Maternal Disease during Pregnancy and Myopia in the Child. P. A. Gardiner and G. James.
Acute Retinal Vascular Proliferation. J. A. Chivers.
Bilateral Retinal Detachment Following Carotid-cavernous Fistula. J. F. Cogan.
Ophthalmoscopic Attachment for the Diagnosis of Eccentric Fixation. H. H. Massie.

GUT.—Issued quarterly (£3 annually). The new issue (Vol. 1, No. 1) includes:

Foreword. Harold C. Edwards.
History of the British Society of Gastroenterology. Thomas Hunt.
Early Investigations of Haematemesis. G. N. Chandler, A. D. Cameron, A. H. Nunn, and D. F. Street.
The Incidence of Chronic Peptic Ulcer Found at Necropsy. Geoffrey Watkinson.
Observations on Blood Group Distribution in Peptic Ulcer and Gastric Cancer. R. Doll, B. F. Swynnerton, and A. C. Newell.
The Effects of Corticotrophin and Corticoids on Secretion from Denervated Gastric Pouches in Dogs. S. D. Clarke, D. W. Neill, and R. B. Welbourn.
Serotonin, Bananas, and Diarrhoea. A. M. Connell, E. N. Rowlands, and P. B. Wilcox.
Coeliac Disease: Histopathological Findings in the Small Intestinal Mucosa Studied by a Peroral Biopsy Technique. Margot Shiner.
A Study of the Pancreatic Response to Food after Gastrectomy in Man. T. J. Butler.
Intestinal Pseudo-obstruction with Steatorrhoea. J. M. Naish, W. M. Capper, and N. J. Brown.
Diagnostic Significance of D-Xylose Excretion Test. D. Fowler and W. T. Cooke.
Multiple Endocrine Adenoma Syndrome. W. T. Cooke, D. I. Fowler, R. Gaddie, E. V. Cox, M. J. Meynell, and D. Brewer.
Volvulus of the Small Intestine in Adults. C. H. Talbot.
Annual Meeting of the British Society of Gastroenterology.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, April 11

MEDICAL RESEARCH COUNCIL.—At National Institute for Medical Research, Mill Hill, London, N.W., 5 p.m., Dr. F. Jacob (Paris): Genetic Control of Regulation Mechanisms in Bacteria.

Tuesday, April 12

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Dr. D. Kay: Nature of Some Psychoses of Old Age in the Light of Follow-up and Genetic Data.
MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Northern Hospital, Cheetham Hill Road, Manchester, 4 for 4.30 p.m., clinical meeting.
MEDICAL ELECTRONICS DISCUSSION GROUP.—At Institution of Electrical Engineers, Savoy Place, W.C., 5.30 for 6 p.m., discussion to be opened by Lord Fraser of Lonsdale and Dr. R. L. Beurle, Ph.D.: Aids for the Blind.
SOCIETY OF MEDICAL OFFICERS OF HEALTH: HOME COUNTIES BRANCH.—At London School of Hygiene and Tropical Medicine, 3 p.m., Professor F. Bergel, D.Sc., F.R.I.C.: New Developments in the Field of Carcino-chemotherapy (illustrated).

Wednesday, April 13

MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Departments of Pathology and Bacteriology, Clinical Sciences Building, York Place, 4.30 for 5 p.m., laboratory meeting.
PLYMOUTH MEDICAL SOCIETY.—2.30 p.m., visit to Plymouth City Waterworks.

Thursday, April 14

ALFRED ADLER MEDICAL SOCIETY.—At Royal Society of Medicine, 8 p.m., Dr. M. Glatt: Community Living and Group Therapy in the Treatment of Alcoholism.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—4.30 for 5 p.m., Joseph Henry Lecture by Mr. Leon Gillis: Arm Prostheses and Appliances. Their Functional Value in Industry.

APPOINTMENTS

BIRMINGHAM REGIONAL HOSPITAL BOARD.—J. L. Crammer, M.R.C.S., L.R.C.P., D.P.M., Whole-time Consultant Psychiatrist to All Saints' Hospital and Uffculme Early Treatment Centre, Birmingham; F. D. Honneyman, M.D., M.R.C.P.Ed., M.R.C.P.I., Part-time Consultant Physician with experience in Geriatrics to Wolverhampton and Walsall Groups of Hospitals; J. Newcombe, M.B., B.S., D.P.M., Whole-time Consultant Psychiatrist to Monyhull Hall Hospital, Birmingham.
SWEETNAM, D. R., M.B., B.Chir., F.R.C.S., Assistant Orthopaedic Surgeon (Consultant).

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Champion.—On March 23, 1960, to Valerie, wife of Dr. Alan Champion, of "Lawnswood," Ventnor, Isle of Wight, a brother for Helen and Rosemary—Stephen Arnold.
Livingstone.—On March 14, 1960, at Vancouver, British Columbia, Canada, to Greta (formerly Kaddish), M.B., Ch.B., and Charles Livingstone, M.R.C.P., D.C.H., of 6652, Granville Street, Vancouver, twin daughters.
Spry.—On March 27, 1960, at British Military Hospital, Hostert, B.F.P.O.40, to Richenda (formerly Maw) and Major W. B. Spry, R.A.M.C., a brother for Jonathan and Tamsin—Alasdair John Bennett.

DEATHS

Couchman.—On March 18, 1960, at Morland, Ferndown, Dorset, Hugh John Couchman, M.B., B.Ch., aged 73.
Marston.—On March 18, 1960, Wilfred Harvey Marston, O.B.E., T.D., M.B., Ch.B., of 691, Coventry Road, Small Heath, Birmingham, Warwicks.
Symons.—On March 19, 1960, in St. George's Hospital, Hyde Park Corner, London, S.W., Linda Symons, M.R.C.S., L.R.C.P., of Bradford, Yorks.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Penicillin and Streptococcal Tonsillitis

Q.—*For how long, and in what form and dosage, should penicillin be given to treat the common streptococcal infections—for example, a streptococcal throat? Or is antibiotic treatment unnecessary, except to deal with the more severe forms of the illness?*

A.—There is a difference of opinion about the treatment of tonsillitis. In my opinion, when a child develops a tonsillitis (not merely a mild sore throat in conjunction with coryza), a throat swab should be taken to determine whether haemolytic streptococci are present, because it seems that less than half of cases of tonsillitis can be ascribed to the streptococcus. If the swab is positive the child should be given penicillin, not only because it shortens the course of the illness and the duration of the carrier state but chiefly because it greatly reduces the incidence of complicating rheumatic fever and nephritis.

The most pleasant treatment for a child is phenoxymethyl penicillin by mouth in a dose of 125 mg. six-hourly for 10 days: the disadvantage is that doses are apt to be missed at night, and it is expensive (approximately 13s. 9d. for the 10 days). The alternative is one dose of "triplopen" by intramuscular injection (cost 2s. 1d.).

Corticosteroids for Alopecia Universalis

Q.—*Are corticosteroids effective in the treatment of alopecia universalis, and, if so, would they be suitable for a child aged 11? Which corticosteroid is recommended?*

A.—Local injection of hydrocortisone into the scalp and administration by mouth of the more modern steroid hormonal preparations such as triamcinolone commonly cause regrowth of hair in universal alopecia. The hair falls again when the treatment is withheld or dosage reduced. Shelley[1] recently reported a patient with this condition in whom such treatment was continued over a period of 18 months, but the hair fell again as soon as the dosage of triamcinolone was reduced.

It is clearly unwise to use these powerful remedies over long periods for such an affection as alopecia, more particularly in children, when they are unlikely to be permanently effective. The prognosis in universal alopecia is generally bad, but the general health is not impaired.

REFERENCE

[1] Shelley, W. B., Harun, J. S., and Lehman, J. M., *A.M.A. Arch. Dermat.*, 1959, **80**, 433.

Supersonic Dental Drills

Q.—*Are the supersonic vibrations from the new "airotor" ultra-high-speed, air-driven turbine dental drills harmful to the odontoblasts and nerves in the pulp?*

A.—All experiments carried out so far indicate that the main danger to the pulp (all elements) is from heat. Adequate cooling of the bur is therefore of the utmost importance. Reports by different workers on the "supersonic" effects have been conflicting. Pathological changes of varying degrees have been reported by some, whereas others find no changes in excess of those produced by conventional low-speed drilling. "Rebound" damage on the opposite side of the pulp to the cavity has also been observed. All recent work on this subject has been admirably summarized with full references by I. R. H. Kramér.[1]

REFERENCE

[1] Kramer, I. R. H., *Int. dent. J.*, 1959, **9**, 435.

Snuff and Coryza

Q.—*As a snuff-taker, it is my impression that the habit confers considerable immunity against coryza. Is it possible that, either by virtue of its action on reducing the sensitivity of the nasal mucosa or by a bactericidal effect, this impression may be correct?*

A.—Snuff consists of powdered tobacco mixed with certain essential oils, and these all have mild antiseptic properties. Tobacco itself also contains antiseptic substances, such as formaldehyde, which normally appear in tobacco smoke, but whether these are liberated when tobacco is taken as snuff is uncertain. Persistent snuff-taking probably produces changes in the nasal mucosa. Whether or not these changes would make the mucosa a less satisfactory milieu for the growth of the common cold virus it is impossible to say at the present time. On the other hand, it is an irritant, and could have the opposite effect, but this would be more likely to apply to the casual snuff-taker.

Occipital Pain in Cervical Distension

Q.—*Neuwirth[1] describes pain from a cervical disk lesion which may sometimes simulate migraine. What is the value of neck traction, and is it possible that division of the great auricular nerve and other measures would give relief in the syndrome?*

A.—A cervical disk lesion in the upper part of the cervical spine may well give rise to occipital pain through the normal pathways. Neck traction does seem to produce symptomatic relief. Although it often fails, a significant proportion of patients find early comfort from this procedure and the attacks are perhaps shortened. In such a variable condition the assessment of any method of therapy is extremely difficult. When the lesion is due to pressure on a nerve root from a prolapsed disk or osteoarthritic joint, division of the nerve for relief of pain would have to be proximal to the pressure to be effective. This would involve a laminectomy, with all its hazards, and nerve root decompression, in which case it would probably be unnecessary to divide the nerve root as well as decompress it.

REFERENCE

[1] Neuwirth, E., *Ann. Intern. Med.*, 1952, **37**, 75.

Ankylosing Spondylitis and Pregnancy

Q.—*A 26-year-old woman, married for six years, was found to have ankylosing spondylitis shortly after her marriage. She was advised to postpone pregnancy. Her general condition has been well maintained, although the disease has phases of greater activity. The last was two years ago. Is it now safe for her to embark on pregnancy?*

A.—It is never "safe" to embark on pregnancy, but many women with ankylosing spondylitis have had children without any long-lasting ill effects. Provided that adequate care is taken during pregnancy, and particularly that there is a high calcium diet with some slight increase in vitamin D intake to prevent osteoporosis, pregnancy and delivery should be uneventful. A short phase of increased disease activity may sometimes follow but it is usually self-limited and can be dealt with by such analgesics as phenylbutazone. This question is really determined more by the attitude of the married couple towards children than by the effects of pregnancy on spondylitis, and if they want a child they should be encouraged to have one, particularly if the woman is in a position to get some help with the child to spare her any increased work.

Pulmonary Moniliasis

Q.—*What is the present treatment for pulmonary moniliasis? In what percentage of cases is treatment with intravenous gentian violet successful?*

A.—In the great majority of cases moniliasis of the lower respiratory tract is secondary to some underlying disease, and the first step, therefore, in the management of a case of respiratory disease, in which the continued presence of

Candida albicans in the sputum leads to suspicion of moniliasis, is to take every step to exclude other diseases. It should not be forgotten also that the use of antibiotics predisposes to invasion by this organism. The only reference I have been able to find to the use of intravenous gentian violet in broncho-pulmonary moniliasis dates from 1928,[1] and on general principles it would seem very unlikely that an effective dose of this agent could be brought by this route to the site of what is essentially a surface infection of the bronchial tree. It would seem more logical to attempt to treat the condition by inhalation of a nebulized solution. The strength of solution used in this way should be determined by the patient's tolerance. Probably 1:5,000 would be tolerated. If, as is likely, there are associated lesions of the upper respiratory tract, these could, of course, be treated as usual by local applications of gentian violet. In a case in which there is good reason to suspect a serious primary involvement of the lungs or in which secondary moniliasis is an important complicating factor, it would be worth trying the effect of nystatin, although this antibiotic is poorly absorbed when given by mouth. 500,000 units four times a day would be a suitable dosage.

REFERENCE

1 Stovall, W. D., and Greeley, H. P., *J. Amer. med. Ass.*, 1928, **21**, 1346.

Paper Disks for Phage Typing

Q.—*Are paper disks for phage typing of staphylococci,[1] similar to paper disks used for antibiotic sensitivity, available? Are they satisfactory? If so, where can they be obtained?*

A.—These disks are not available in this country, and they are not regarded with favour by those expert in this type of work. They have to be left on the surface of the medium, and lysis is seen only as a halo surrounding them. This deprives the test of its quantitative aspect: as usually performed it employs concentrated and dilute phage, which may produce either confluent lysis or isolated plaques: lesser degrees of susceptibility to phage would be undetected by the disk method.

REFERENCE

1 Mora, E. C., and Eisenstark, A., *J. Lab. clin. Med.*, 1958, **51**, 802.

NOTES AND COMMENTS

Desensitization to Streptomycin.—Dr. HAROLD WILSON (London, W.1) writes: I am interested in your reply in "Any Questions?" (*Journal*, February 27, p. 665) to a query about desensitization to streptomycin. Crofton[1] distinguishes clearly between patients sensitized to streptomycin as a result of treatment and nurses who become sensitive as a result of handling the drug. He finds that desensitization is comparatively easy in the case of the former but difficult and sometimes hazardous in that of the latter. Your expert suggests that nurses should be given an initial dose of 10 μg., followed, if there has been no reaction, by 100 μg. In these highly sensitive subjects reactions are apt to occur to extremely low doses of streptomycin. One of Crofton's cases developed a rash after doses of 50 μg. and 100 μg. given intramuscularly, while Cohen and Glinsky[2] reported a very alarming reaction with damage to the labyrinth after an initial dose of 100 μg. In my own experience[3] an extensive eruption occurred after doses of 20 and 40 μg. given intramuscularly. I would suggest a much more cautious scheme of desensitization for nurses, and advise an initial dose of 2 μg. followed by daily doses of 5, 10 and 20 μg. Steroid cover is likely to reduce the reaction but not to suppress it completely. It is doubtful if antihistamines have any influence on a purely eczematous condition. Desensitization is not always permanent.

REFERENCES

1 Crofton, *Brit. med. J.*, 1953, **2**, 1015.
2 Cohen and Glinsky, *J. Allergy*, 1951, **22**, 63.
3 Wilson, H., *Brit. med. J.*, 1958, **1**, 1378.

OUR EXPERT replies: The original question was, "Is it possible to desensitize a patient who had a reaction after being given streptomycin and dihydrostreptomycin systemically?" In the answer I gave details of the skin testing and desensitization of such a patient (sensitized by injection) with references to the literature. However, as is quite clear from the literature and clinical practice and as is again emphasized by Dr. Wilson, those sensitive by contact, such as nurses and dispensers, are in quite a separate and more sensitive group than those sensitized by injection.

It was because of the risk of some readers not appreciating this and possibly applying the dosage advised for the questioner's case to a nurse or dispenser, that I called attention to the other more sensitive group. I wrote: "In patients very allergic to streptomycin, such as nurses or dispensers hypersensitive by contact, skin-testing should start with 10 μg. . . . In patients . . . who develop sensitivity during treatment . . . 10 mg. is advised. . . . Desensitization starts with a test dose just below that which gives a positive reaction, and, in the absence of any reaction, the dose is subsequently doubled each time. . . ."

I suggested 10 μg. as an initial test dose because I could find no record of a dangerous reaction having occurred with this dose. It must be emphasized, however, that the dose used in an initial skin-test must always be judged very carefully in relation to the history in that particular case. I would agree with Dr. Wilson that in the exceptional patient an even smaller dose might be used as a starting test dose. I would also like to emphasize that, if a marked local reaction occurs with a skin-test dose such as 10 μg., later skin-testing should be carried out with a smaller dose, 5 μg. or 2 μg., until the dose at which a positive reaction is just obtained is known. Desensitization should then begin with a dose just below that which only just gives a positive reaction. I would agree that a steroid cover would reduce any reaction but not suppress it completely, but cannot agree that antihistamines have no suppressive action.

I sincerely welcome Dr. Wilson's contribution on this important and difficult subject. Had the original question been on this specially sensitive group I would have certainly dealt with it in more detail and brought Dr. Wilson's important personal contribution to the notice of readers again.

Ultrasonics in Physiotherapy.—Dr. E. PHILLIP (Wellington, New Zealand) writes: Under "Any Questions?" (*Journal*, November 7, 1959, p. 968) you answer a question on ultrasonics in physiotherapy. Ultrasonic waves certainly produce heat through friction at the junction of various tissues with different densities. This, though, is only a side action. Sound waves produce a physical movement of molecules. A micro-massage with rapid intense movement of particles produces an intense intra- and peri-cellular movement of fluid which removes waste products and helps healing. The one danger is the possibility of cell disruption by too strong an intensity inaccurately used. Ultrasonics used by a skilled operator under the guidance of a competent physician for suitable disabilities are a valuable treatment and take their place among the tools of the physiotherapists. They have been used in Wellington increasingly over the last few years.

OUR EXPERT replies: This is an interesting comment. Certainly the increasing use in Wellington is the reverse of the situation in England, where ultrasound was tried and found to have few indications. In England ultrasonics have been used less and less over the last few years.

Correction.—The obituary of Dr. Barbara G. R. Crawford (March 26, p. 972) gave her maiden name as Rutherford instead of Rutherfurd. Dr. Crawford is survived by a daughter and two grandsons (and not by two sons as stated in the obituary).

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